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CYST OF THE COMMON DUCT

BEVERLY CHEW SMITH, M.D.

NEW YORK

A cyst or idiopathic cystic dilatation of the common duct is comparatively rare. The number of cases in an individual physician's experience is too small to formulate a definitive plan of treatment. The literature of the past is lacking in follow-up reports. Recent chemical methods for combating bleeding in cases of jaundice have possibly changed the surgical emergency of this condition. Most reported cases lack laboratory observations of the chemistry associated with jaundice.

I have been able to collect 181 cases from the literature. Two additional cases are here reported from the Presbyterian Hospital. They are the only cases of the kind on file among the records of 757,000 cases.

Many factors have been advanced as the cause of this condition. The most logical encountered is that given by Yotuyanagi, namely—the inequality of proliferation of the epithelial cells when the common duct is a solid cord of cells and while it is becoming a patent tube. This occurs about the eighth week of fetal life.

It is of interest that most of these cases have occurred in female patients before 25 years of age. A number have been pregnant when the cyst became clinically obvious.

The cyst wall has frequently been fibrous tissue without lining epithelium.

The only case found with a long follow-up was that of Judd and Greene in which the cyst was anastomosed to the duodenum on Feb. 4, 1927. This patient replied to a questionnaire from the Mayo Clinic in February 1932 that she was perfectly well. However, on Jan. 4, 1940, her local physician sought by letter to learn what operative procedure had been performed on her because "at the present time she is having symptoms similar to gallbladder disease." This thirteen year follow-up report thus leaves one in doubt as to the true condition existing in this patient at present.

Read at a combined meeting of the New York Surgical Society and the Philadelphia Academy of Surgery, New York, Feb. 12, 1941.

From the Surgical Service, Presbyterian Hospital, and the Department of Surgery, Columbia University College of Physicians and Surgeons.

REPORT OF CASES

CASE 1.—M. D., a 20 year old unmarried woman, was admitted to the Presbyterian Hospital on Sept. 23, 1940, complaining of a mass in the right upper part of the abdomen which had steadily enlarged in the past five weeks, jaundice of three weeks' duration, itching, loss of appetite, loss of weight and discomfort in the region of the abdominal mass. She had always lived on Long Island. Her babyhood was normal. In childhood she was exposed to her mother, who died of pulmonary tuberculosis in 1927, and one sister, who had the disease but recovered.

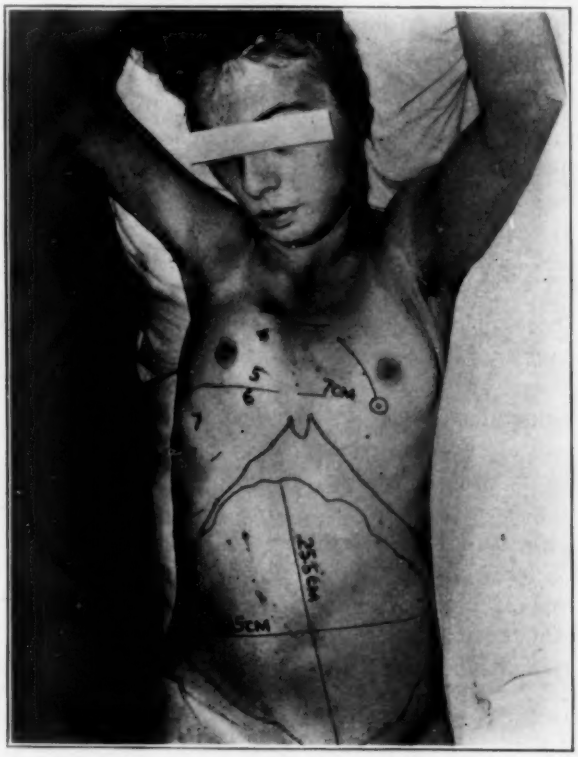

Fig. 1.—Photograph showing outline and size of cyst.

Her past health had been excellent except for an attack of painless jaundice lasting one month in 1932 at the age of 12. She was deeply jaundiced at that time; her skin itched, but she could not recall having had clay-colored stools. Other than this she had always been healthy and active and had engaged in strenuous outdoor exercise.

About Aug. 16, 1940, she noticed a hard nontender mass in the right upper part of the abdomen, measuring about 2 by 2 inches (5 by 5 cm.), just below the costal margin. In a week, it doubled in size. In two more weeks, it filled the right half of the abdomen. During the second week that she noticed the mass she became jaundiced. Her skin itched, and her jaundice steadily deepened. Three weeks after she noticed the mass and one week after the onset of jaundice,

she noted clay-colored stools. She was never really acutely ill and was nauseated and vomited only after taking certain fatty foods.

When she first noted the mass, she felt a dull aching abdominal pain in the region of the mass, but this subsided and did not recur. She was constipated and lost 30 pounds (13.6 Kg.), and her appetite failed. There were no tarry stools. Her menstrual periods were normal.

On admission, the temperature was 100 F.; the pulse rate, 100; the respiration rate, 20. The blood pressure was 124 systolic and 100 diastolic. She was thin, deeply jaundiced and chronically ill. There were many scratch marks over the

Fig. 2.—The cyst (outlined by arrows) has pushed the stomach to the left and the duodenum posteriorly so that it has been hidden by the stomach.

whole of her body, and on the left wrist there was an area of ecchymosis 3 by 9 cm., which occurred without a history of trauma.

A nontender firm slightly irregular mass 25.5 by 30.5 cm. which gave the sensation of containing fluid extended from the right costal margin to the right anterior superior iliac spine, beyond the umbilicus and could be balloted in the right flank. Its lower edge moved with respiration. The liver was discernible to percussion to the fifth interspace in the midclavicular line and to the ninth rib in the midaxillary line. Rectal examination was negative except that the feces were black. There were no hemorrhoids. The pelvic adnexa on rectal examination were normal. A diagnosis of cyst of the right upper part of the abdomen was made; the cyst was considered to be pancreatic, hepatic, choledochal or mesenteric.

The significant laboratory findings before and after operation may be summarized conveniently as follows:

Initial blood study: red cell count, 3,000,000; hemoglobin content, 55 per cent; white cell count, 11,900, with 55 per cent polymorphonuclears and 34 per cent small lymphocytes; Kline test, negative; serum cholesterol, 248 mg. per hundred cubic centimeters.

9/25/40 Bleeding time, 30 seconds; clotting time, 3 minutes.

9/26/40 Transfusion of 500 cc.

9/29/40 Transfusion of 500 cc. (citrated blood).

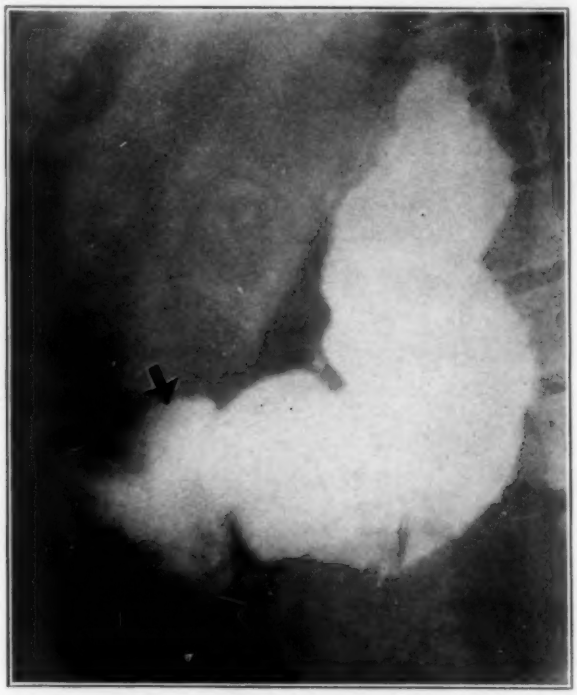

Fig. 3.—Arrows indicate the degree of dilatation of the duodenum.

11/30/40 Two transfusions of 500 cc. each.

9/27/40 Cystic fluid: protein, 0.34 per cent; bile acid +; amylase and lipase 0; bilirubin 0.

9/28/40 Amylase and lipase present in bile drainage.

11/ 7/40 Protease 0; carbon dioxide, 55 volumes per hundred cubic centimeters.

9/24/40 Cephalin flocculation test, negative.

1/ 6/41 Cephalin flocculation test, negative.

11/ 7/40 Benzoic acid liver test: 3.2 Gm. excreted in urine.

1/21/41 Bromsulfalein liver test: 50 per cent retained at end of five minutes; trace in blood at end of thirty minutes.

11/19/40 Blood calcium, 10.4 mg. per hundred cubic centimeters; nonprotein nitrogen in blood, 22 mg. per hundred cubic centimeters.

11/25/40 Prothrombin time normal.

1/24/41 Urobilin output in stool, 8,500 units per day.

1/ 6/41 Red blood cell count, 3,600,000; hemoglobin content, 80 per cent; white blood cell count, 4,300, with 21 per cent polymorphonuclears and 61 per cent small lymphocytes; agglutination test with sheep red blood cells in 1:8 serum dilution (Forssman antigen), negative for mononucleosis.

Fig. 4.—The cyst (outlined by arrows) has displaced the colon, as outlined by the enema of barium sulfate, into the pelvis.

9/29/40 Bile drainage, 310 cc.

10/ 1/40 Bile drainage, 800 cc.

10/ 5/40 Bile drainage, 500 cc.

9/24/40 Urine: bile 4+.

10/27/40 Urine: bile 0.

9/24/40 Stool: bile 0; guaiac 4+.

The roentgen studies before and after operation may be summarized as follows:

9/25/40 *Gastrointestinal series:* The abdominal mass displaced the stomach and the duodenum forward and to the left and the tranverse colon downward. The mass could not be separated from the liver.

9/26/40 *Right intravenous pyelogram:* The mass filled the right portion of the abdomen. The outline of the right kidney was indistinct but normal. The left kidney was not clearly seen. The small intestines were pushed to the left. The right ureter, the renal pelvis and calices were well filled with dye. The ureter was normal. There was slight dilatation of the right renal pelvis and calices.

10/10/40 Two weeks after marsupialization of cyst: The cyst sac was filled with hippuran; it was triangular and measured 15 by 7 cm. A narrow tract on its superior and lateral border seemed to be in direct relation with the hepatic ducts. No opaque fluid entered the duodenum. The cyst held 80 cc.

TABLE 1.—*Summary of Data from Studies of Blood of Patient M. D.*

Date	Serum Bilirubin Mg. per 100 Cc.	Phosphatase, Mg. per 100 Cc.	Phosphatase (Bodansky Units per 100 Cc.)	Hematocrit Value	Plasma	
					Specific Gravity	Protein, Per Cent
9/24/40	20	3.7	19.5	30.8	1.0239	5.78
9/26/40	31	3.7	22.1	....	.....	....
9/27/40	30	3.8	21.8	....	.....	....
(First operation *)						
9/28/40	20	...	....	37.1	1.0223	5.4
9/29/40	15	...	....	36.2	1.0220	5.14
10/ 7/40	....	...	....	40.9	1.0280	7.18
10/15/40†	6.1	...	....			
10/18/40	5.2	...	....	....	.....	7.3
10/25/40	3	...	....			
10/31/40	2.7	...	....			
11/13/40	1.3	...	....			
11/30/40	...	...	....			
(Second operation ‡)						
12/ 9/40	Negative	3	3.3			
12/30/40	....	3.4	9.4			
1/ 6/41	Negative	3.3	6.6			

* Marsupialization of the cyst.

† Administration of desiccated hog bile in capsules (Parke-Davis desicol) started; one capsule three times a day increased to thirty-three capsules per day. Each capsule contains 5 grains (0.325 Gm.) of desiccated bile, equivalent to 2.5 cc. of whole fresh bile.

‡ Anastomosis of the cyst to the duodenum.

10/18/40 Intravenous injection of soluble iodophthalein failed to reveal a gallbladder shadow.

10/20/40 Hippuran in the cyst showed a slight diminution in the size of the cyst since similar procedure ten days before and no communication with the duodenum. The cyst held 30 cc.

1/ 2/41 Thirty-two days after the cyst was anastomosed to the duodenum. Gastrointestinal series: The duodenum showed slight constriction at the cyst anastomosis site. The cyst filled and emptied readily through the anastomosis. Barium sulfate proceeded from the duodenum into the small intestine normally. There was a slight barium residue in the cyst at twenty-four hours.

1/11/41 Roentgenogram of the chest essentially negative.

1/29/41 Gastrointestinal series: Barium sulfate failed to enter the cyst.

The patient was given bile salts, vitamin K and a transfusion and because of rising serum bilirubin was subjected to operation on September 27.

First Operation.—The abdomen was opened with infiltration local anesthesia through a 2 inch (5 cm.) retracted upper right rectus incision. The patient was too ill and deeply jaundiced to permit of other than a palliative and exploratory procedure. A cystic mass was encountered which was too large to be delimited.

Fig. 5.—The cyst was injected with hippuran twelve days after marsupialization. It held 80 cc. The hepatic radicles partially fill at the upper right margin of the cyst.

It was aspirated. The first white mucoid fluid was followed by dark brown fluid without odor. A sucker aspirated 5,200 cc. of similar fluid.

The duodenum lay anterior on and to the left of the cyst wall; the small intestines were pushed to the left into the pelvis; the transverse colon was below it and also in the pelvis; the stomach was upward and to the left. The gallbladder was in its normal position; it was edematous and about twice normal size. The liver was not apparently cirrhotic; its lobes were normal. About 100 cc. of bile-stained clear nonodorous fluid was recovered from the peritoneal cavity.

The cyst was opened, explored and found to have a smooth wall without calcification or calculi. It extended to the hilus of the liver. No communication could be made out with the hepatic ducts, the gallbladder or the duodenum, and no bile drained into the cyst while it was being observed. The pancreas could be felt through the posterior wall of the cyst. The foramen of Winslow was patent. The common duct as such could not be identified in the gastrohepatic omentum. Because the nature of the cyst could not be determined, a piece of the wall was taken for pathologic examination. The cyst was marsupialized by suture to the anterior rectus sheath, and a rubber tube was sutured into it. The patient stood

Fig. 6.—Arrows indicate the retention of barium sulfate in the cyst twenty-four hours after barium sulfate was given by mouth for gastrointestinal study. This study was made thirty-three days after the cyst had been anastomosed to the duodenum.

the procedure well. She was given a second transfusion on her return to the ward with 500 cc. of citrated blood.

Pathologic Examination.—The cyst wall consisted of a piece of greenish yellow tissue, one surface of which was smooth and glistening; the other surface showed hemorrhagic foci. It was fixed in Bouin's fluid. Microscopic examination revealed the cyst wall to be composed of dense fibrous tissue. It was avascular and showed

a mild polymorphonuclear infiltration. The inner surface was covered by a layer of acidophilic coagulin. There was no evidence of epithelium.

Nine hours after this operation, clear golden yellow bile began to drain from the cyst and continued to do this until a second anastomosing operation was done on November 3. For thirty-seven days between the operations, the patient's stools

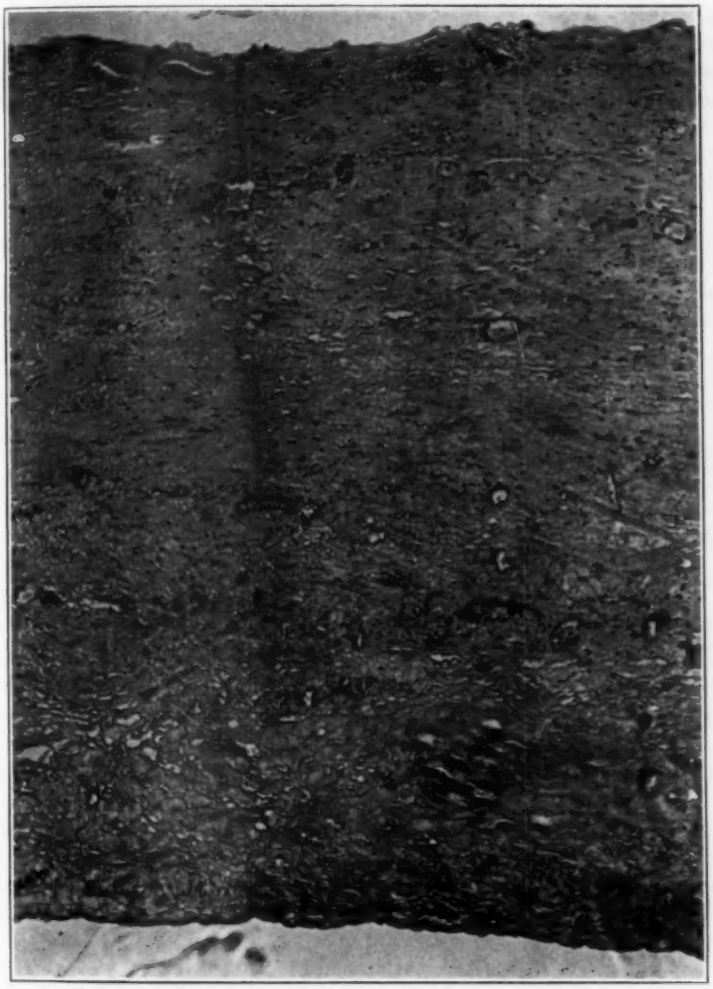

Fig. 7.—Photomicrograph of the cyst wall. For description see text.

were continuously free of bile. The bile output varied from 300 to 800 cc. in twenty-four hours, averaging 500 cc. There was little excoriation of the skin about the cyst opening.

Postoperative Course.—The jaundice gradually diminished until the serum bilirubin on the fifty-third postoperative day was 1.3 mg. per hundred cubic centimeters. The urine phosphatase and cholesterol became normal. The cyst continued

to drain the entire biliary output. No communication could be established by roentgen examination with the duodenum, but a suggestion of the hepatic ducts was noted on one occasion. The stool was negative for bile.

The patient was given vitamin K and bile salts, and a study of fat digestion with and without bile salts was made (table 2). She gained 8 pounds (3.6 Kg.) and became ambulatory.

Second Operation.—Because of continued bile drainage an anastomotic procedure was deemed necessary, and on November 30, with the patient under anesthesia induced with nitrous oxide and oxygen through a transverse upper right rectus incision the abdomen was opened by Dr. Allen O. Whipple, Dr. Beverly C. Smith assisting, and the following observations were made:

The cyst was a large collapsed sac measuring roughly 12 by 18 cm. and extending from the portal fissure to the opening of the cyst in the anterior

TABLE 2.—*Fat Absorption in a Case of Complete Bile Fistula Following Marsupialization of a Cyst of the Common Bile Duct* *

Date	Weight of Patient, Lb.	Fat Consumed,† Gm.	Fat in Stool, Gm.	Fat Absorbed, Per Cent	Bile Capsules, per Day ‡
10/24/40	85 (38.6 Kg.)	50	48	4	18
10/29/40	87 (39.5 Kg.)	100	75	25	18
11/12/40	90 (40.8 Kg.)	100	84	16	33
11/18/40	91½ (41.5 Kg.)	100	67.5	33	33
11/30/40	Operation: anastomosis of the cyst with the duodenum				
12/20/40		33.7	4.87	86	
1/22/41		66	6.7	..	
1/23/41		66	6.7	90	
1/24/41		66	6.7		

* The following note on these fat absorption studies was made by Dr. Louis Bauman: "While I have made no exhaustive search of the literature, my impression is that this patient afforded a rare opportunity to study fat absorption in the complete absence of bile and uncomplicated by other factors, such as partial or complete pancreatic obstruction. The striking difference observed after reentrance of bile into the intestine is ample confirmation of its controlling influence on fat absorption in the human being."

† Weighed diet.

‡ Desicol (Parke, Davis & Co.).

abdominal wall. It was intimately connected with the duodenum and was impossible to separate from this structure without grave risk of creating a fistula in the posterior aspect of the duodenum. It was not certain that the cyst was not adherent to the portal vein. In the upper right portion of the cyst, the opening of the common hepatic duct was seen, and the index finger could be introduced, feeling the opening of the two hepatic ducts into which a probe easily passed into both lobes of the liver. Definite communication between the cyst and the gallbladder could not be established. Aspiration of the gallbladder brought away no bile. No communication could be established between the cyst and the duodenum. The duodenum was opened, and the papilla of Vater was probed with a fine probe which extended into the pancreatic duct well down into the pancreas, but no communication could be established with the cyst from this direction.

It was felt that the procedure of choice was anastomosis of the opening of the cyst with the duodenum. It was felt that attempted excision would endanger the duodenum and the portion of the common duct which the cyst constituted. The cyst was therefore anastomosed to the duodenum with chromic catgut, allowing

an opening of approximately 2 or 3 inches (5 or 7.6 cm.) in each viscus. The fusion between the cyst and the duodenum made a posterior seroserous suture unnecessary. On the anterior wall, a seroserous suture of C silk was placed, and the abdominal wall was closed in layers with catgut and silver wire, because the preoperative wound was infected and possible evisceration was anticipated. The patient received a transfusion of 1,000 cc. of whole citrated blood during the procedure.

Postoperative Course.—The postoperative course was marked by a febrile reaction of 103 F., which became normal by the fourth day. The chest remained clear. Beginning the first week after operation, the patient had a daily rise in temperature to 101 or 102 F. without local signs of infection other than in the wound. The blood cultures and urinalysis were negative. A roentgenogram of the chest showed normal lungs. There was no clinical evidence of cholangitis. She felt perfectly well and did not complain of pain. The gastrointestinal tract functioned normally. The serum bilirubin became negative; the stools were brown and contained bile; the urine became free of bile; serum phosphatase reached 3.5 Bodansky units on the thirty-first day. The cephalin flocculation test remained negative.

On the thirty-ninth postoperative day, the blood count revealed: 3,600,000 red blood cells with 80 per cent hemoglobin, and 4,300 white blood cells with 33 per cent neutrophils, 1 per cent eosinophils, 8 per cent monocytes and 58 per cent lymphocytes. An agglutination reaction with Forssman's reagent was negative for mononucleosis.

Wound healing was complicated by numerous superficial sinuses around the silk sutures which were successively emitted from the wound. A wound culture revealed a nonhemolytic Staphylococcus aureus. It was thought that this was largely responsible for the patient's elevation of temperature. By the forty-sixth day, the temperature had returned to normal.

The bacteriologic findings may be summarized as follows:

9/30/40	Culture from scratch marks in skin: hemolytic Staphylococcus aureus and Streptococcus viridans. Free peritoneal fluid: no growth. Cyst fluid: no growth.
10/15/40	Bile draining from cyst: Salmonella group (gram-negative rods).
10/16/40	Bile draining from cyst: 330,000 organisms per cubic centimeter; after standing twenty-five hours in icebox, 1,600,000 organisms per cubic centimeter.
11/20/40	Bile from cyst: hemolytic Bacillus coli; no anaerobes.
11/22/40	Sulfathiazole given, 7 Gm. for one day; severe nausea; drug stopped.
12/ 4/40	Wound culture at second operation: nonhemolytic B. coli, Staph. aureus, no anaerobes.
12/ 6/40	Wound culture: nonhemolytic Staph. aureus.
1/ 7/41	Blood culture: no growth.
1/ 9/41	Urine culture: B. coli in clean noncatheterized specimen.

On the thirty-fourth day after the second operation a gastrointestinal series of roentgenograms showed barium sulfate entering and leaving the cyst through the anastomosis with a small twenty-four hour residue in the cyst; the meal proceeded normally down the small intestine during the examination. On the fifty-third day, a bromsulfalein test showed 52 per cent retention in five minutes and only a trace in thirty minutes, indicating normal liver function.

The patient became ambulatory on the forty-second day after operation and gained an average of 1 pound (0.5 Kg.) a week for four weeks previous to discharge, at which time she weighed 92 pounds (41.7 Kg.). Her normal weight before the onset of this illness was 114 pounds (51.7 Kg.). Studies of fat absorption during the four weeks after operation showed that 90 per cent of the fat ingested was absorbed compared to only 4 per cent of a measured amount absorbed when all of the bile was coming through the fistula.

The postoperative course was uneventful and comfortable. She was discharged to a convalescent home on the sixty-second day with a small granulating superficial wound. At the time of writing, her wound is solidly healed except for a superficial sinus at each end which probably harbors a silk suture. The red blood cell count is 4,240,000 with 82 per cent hemoglobin, and the white blood cell count is 9,200 with 36 per cent polymorphonuclears, 41 per cent small lymphocytes, 17 per cent large lymphocytes and 6 per cent monocytes.

At the time of a follow-up examination, Oct. 15, 1941, the patient was symptomless; she weighed 121 pounds (54.9 Kg.) and had returned to her former secretarial position.

CASE 2.—M. M., a woman 28 years old, was admitted to the Presbyterian Hospital on Jan. 30, 1916, with the following history:

Since the age of 18, when she was at boarding school, she had irregular attacks of dull aching abdominal pain, jaundice, clay-colored stools and malaise. At times she would be free of symptoms for months. In 1910 (six years before admission), she had a severe attack of jaundice which lasted three weeks. Several less severe similar attacks occurred between her first pregnancy, which resulted in a spontaneous abortion at two months, and her second pregnancy, which was marked by attacks of severe pain and jaundice. She described the pain of her attacks as occurring "in the middle" of her and not radiating. Local physicians regarded her condition as gallstone colic, but operation was twice postponed because of her pregnancies. In August and October of 1915, she had particularly severe attacks of pain and deep jaundice. Surgeons thought they felt her gallbladder during these attacks.

Her past history was negative except for scarlet fever and diphtheria when she was 3 years old. In 1915, she had a tonsillectomy done at the Mayo Clinic, after which she had severe postoperative hemorrhage, which was controlled by the usual methods. Her early girlhood was healthy, vigorous and free of illnesses. Her mother and father, a brother and a sister were living and well. The patient had one living normal child.

First Operation.—Operation was performed on Jan. 31, 1916, by Drs. George Brewer and Adrian Lambert with the patient under anesthesia induced with nitrous oxide and ether.

The gallbladder was soft and flaccid. No stones were felt in any of the biliary ducts. There was a tense cystic mass the size of a grapefruit (about 12 to 15 cm. in diameter) in the head of the pancreas. This cyst was aspirated with a trocar after it was exposed by opening the lesser sac through the gastrohepatic omentum. The cyst wall was friable and about 1/16 inch (0.16 cm.) thick. The aspirated fluid resembled old blood and was thought not to have been bile. The cyst lay to the left of the ducts, was adherent to and communicated with the common and cystic ducts at about their juncture. The cystic duct was elongated, tortuous and enlarged. The stomach and the duodenum were normal.

Procedure.—The peritoneal cavity was entered through an upper right rectus incision. The gastrohepatic omentum was incised; the cyst was exposed, aspirated

and excised from the surrounding pancreas in which it was embedded, down to its connection with the ducts, where the posterior wall was left intact for an area 2 cm. in diameter. This portion of the wall was sutured over a rubber tube which passed into the left hepatic duct. Another rubber catheter was passed downward in the sac toward the common duct and left in situ. From within the cyst no communication with the duct system could be demonstrated by a probe. (No mention is made of communication with the duodenum.) The abdomen was closed in layers. Packing was necessary to control hemorrhage from the site of the excised cyst. The patient was severely shocked by the procedure but reacted to transfusion and other treatments. A week later she was given nitrous oxide to induce anesthesia, and the packing was removed. A bilary fistula persisted. There was no bile in the stool.

Second Operation.—On March 6, 1916, a second operation was performed.

Many firm adhesions were encountered throughout the right upper quadrant of the abdomen. At the base of the sinus tract in the abdominal wall a divided hepatic duct was encountered. There was a collection of several ounces of bile-stained purulent material beneath the liver. The gallbladder was distended with bile. The stomach was adherent under the liver. The adherent duodenum was mobilized.

Procedure.—The previous scar in the right upper quadrant of the abdomen was incised and the abdominal cavity entered. The sinus tract was followed down to the divided ends of the (common) hepatic duct left at the preceding operation. A hole was inadvertently made in the gallbladder just above the ampulla. The divided duct admitted a probe into the right and left hepatic ducts. A small rubber tube was sutured into the lateral portion of the patent common hepatic duct and passed into the rent in the ampullary region of the gallbladder and out the fundus of the gallbladder through the anterior wall of the abdomen. Both openings in the gallbladder were closed with chromic catgut purse string sutures about this tube. A second tube was placed in the fundus of the gallbladder and held there by a purse string of chromic gut. The other end of this tube was placed into the duodenum through a small incision and anchored there by a similar suture with several retaining adjacent serosal sutures of plain gut between these structures. This was done because a probe passed into the hole in the ampullary region in the gallbladder could not be passed into the cystic duct. The upper portion of the cystic duct was never demonstrated. Morrison's pouch was drained, and the abdomen was closed in layers. The patient, who was severely shocked, rallied after a transfusion of 650 cc. of citrated blood.

Pathologic Examination.—The specimen consisted of a portion of a cyst measuring 8 cm. in its greatest diameter. The wall measured 1 or 2 mm. in thickness. On microscopic examination, the cyst wall was found to be composed of loose edematous connective tissue with scattered strands of smooth muscle fibers running through it. The lining consisted of a thin layer of granulation tissue infiltrated with polymorphonuclear leukocytes and round cells with necrotic tissue adherent to it. The wall was vascular with thick-walled vessels. The origin of the cyst was obscure. At one point at a small opening into the cyst, a mucous membrane of cuboidal epithelial cells with underlying short dilated mucous glands in a cellular stroma containing blood vessels was observed and was thought to be from a bile duct. Dr. A. P. Stout made the diagnosis of cyst of the common duct.

Postoperative Course.—The stools remained clay colored. Culture of bile from the sinus tract revealed hemolytic streptococcus. The fluid from the cyst gave a

positive reaction for blood, was negative for bile and showed an increased diastase reaction and a decreased degree of protein digestion by trypsin. A biliary fistula persisted up to and after her discharge on May 15. She slowly regained her strength. The cholecystenterostomy tube passed by rectum two weeks after operation. The stools at that time were dark but subsequently became clay colored and negative for bile. She had severe urticaria during the last week in the hospital.

Third Operation.—There is no record of her course from May 15, 1916 to Oct. 3, 1917, when she was operated on by Dr. W. J. Mayo at Rochester, Minn. Dr. Waltman Walters furnished me with the data hereinafter reported from her record at the Mayo Clinic.

Procedure.—Hepaticocholecystoduodenostomy and partial cholecystectomy were performed through a right rectus incision. On opening the abdomen, dense adhesions of the stomach, the duodenum, the liver and the transverse colon were encountered. It was difficult to get through the adhesions and down to the seat of the trouble. Finally, a way was found into the remnant of the gallbladder, which was extremely thick walled and almost filled with small stones and inspissated foul bile. After evacuating its contents, the surgeon's finger was passed down into the end of the hepatic duct. Apparently the entire main hepatic duct was absent, for the finger passed at once to the right and left main branches. By passing the finger into the right duct about ¼ inch (0.64 cm.), the secondary division of the right duct was reached. Any one of the ducts would admit the finger, and the line of union between the gallbladder and the hepatic duct was the size of a thumb. An enormous quantity of foul bile and a large number of stones of the variety formed in the hepatic ducts were evacuated from the liver ducts. Whether the flow of bile, which previously took place intermittently into the duodenum, passed through some direct connection with the common duct or indirectly through the cystic duct, could not be readily seen; however, no great effort was made to find out, for wherever it was, it was wholly insufficient. After the hepatic ducts were cleaned out as well as possible, the gallbladder was amputated about its middle, and the mucous membrane was dissected out down to a point about ½ inch (1.27 cm.) above the main hepatic duct. The mucous tube, which was about the size of the forefinger, was next loosened and united by a mucomucous suture to an opening made in the duodenum about 2½ inches (6.35 cm.) below the pylorus. A 3 inch (7.6 cm.) section of no. 12 English catheter with lateral eyes was then introduced for a distance of 2 inches (5 cm.) up into the main right hepatic duct; it was passed 1 inch (2.5 cm.) into the duodenum and sutured to the duodenum. It was anticipated that this tube would pass out in due time. It was inserted to insure direct passage until union was complete. The new opening was to be permanent, as the mucous membrane of the gallbladder stump and the duodenum were to be brought in actual contact with the gallbladder tube in its entire circumference. An edge of omentum was placed over the anastomosis. Two rubber tissue drains were used—one above and one below; a short rubber tissue drain was inserted through the fistula.

Postoperative Course.—After operation, the patient's pulse rate went up to 140 the first day of the operation, decreasing rapidly and progressively to the fourth postoperative day when it was normal. At that time the temperature was 99.2 F. It continued at about this level, and the pulse rate remained normal until the early morning of the ninth postoperative day, October 11, when a rapid and progressive rise in the pulse rate and the temperature occurred. On October 12, the temperature was 104 F. by axilla, and the pulse rate was 150. A note on the hospital record

shows that biliary fistula developed on the day of operation. On the eighth day, bleeding occurred from the sinus in the incision, and a transfusion was administered. She died on the tenth postoperative day.

Autopsy.—Autopsy was performed by Dr. W. W. Bissell. The body was that of a well developed markedly emaciated young woman about 30 years of age. There was a recently made, surgically repaired, curving laparotomy wound extending from the ensiform cartilage and extending 5 cm. to the right of the midline. This wound was 16 cm. long and ended at a point 5 cm. to the right and 5 cm. below the umbilicus. About the center there was a gaping area, measuring 3 by 2 cm., and a smaller one just to the right, about 1 cm. in diameter. This area contained dark clotted blood. At a point 2 cm. above this was another opening, also measuring 1 cm. in diameter, and about 8 mm. deep. This presented a reddish base. There was no discharge.

On opening the laparotomy wound, only a slight amount of healing was found. The great omentum was slightly adherent to the anterior parietal peritoneum adjacent to the laparotomy wound, but when discrete fibrinous adhesions all about the lower border of the right lobe of the liver were separated, numerous clots of blood were encountered. All told, there was approximately 500 cc. of blood clot, and after removing these nearly a liter of fluid blood was removed.

Before attempting to ascertain with exactness the lesions about the site of the gallbladder and the bile ducts, the liver, the stomach and the diaphragm were lifted out of the body, together with all the attached abdominal viscera, and were reflected downward in the regular way so that examination proceeded from behind. In this manner, when the hepatic duct was about to be opened, it was learned that it was united to the duodenum. A stump of an opened gallbladder was found at its usual site, but even after a most prolonged search, no cystic duct was discoverable. The common hepatic bile duct was greatly widened. All told, it measured 2 inches (5 cm.) in circumference. Careful search was made for the common bile duct. To begin with, the portal vein was opened and traced out through its main tributaries. It presented no abnormality, and it occupied its usual position and took its usual course. The common bile duct, when examined from behind, usually takes its position just to the right of the course of the portal vein, and search was made for this common bile duct in this position. Dense fibrous tissue was encountered, but no duct could be found.

The pancreas was cut transversely approximately at the junction of the middle third and the tail. By this means, the gaping mouth of the pancreatic duct was found, and the duct of Wirsung was traced throughout its course. Instead of taking the normal course parallel to the long axis of the pancreas and then turning abruptly downward and medianward into the ampulla of Vater to enter the duodenum, this duct turned upward and medianward, and its opening into the duodenum was found without difficulty. Careful search was then made for the opening of the common bile duct in this position, but none was found. The ductus pancreaticus Santorini was then traced, and it was found to bear no relation to a bile duct. It is thus evident that after this careful search no common or cystic bile duct was found. In the case of the cystic duct it is certain that it was either absent or completely obliterated in the fibrous tissue about the gallbladder notch. With regard to the common bile duct the same is true. Yet some remnants of the duct presumably must have functionated. The mucous lining of the duodenum was so softened that no trace of a common duct in the duodenum could be found. The pancreas was enlarged to approximately twice the normal size. In the areolar tissue all about it there was considerable

watery, slightly jelly-like material of inflammatory edema—inflammatory because practically all of the pancreas was replaced by greenish fibrinopurulent necrotic material. Dr. Bissell stated that he had never observed more extensive pancreatitis. All about the pancreas in the areolar tissues, there were numerous small chalky white areas of fat necrosis. This fat necrosis, however, was confined to the immediate vicinity of the pancreas itself.

The liver was of approximately normal size. It was adherent all along its lower border to the diaphragmatic peritoneum, but above it was practically free. On the capsular surface numerous small areas of brownish green discoloration could be seen, and on surfaces made by sectioning, these areas of discoloration were found to be areas of coagulation necrosis. They were discrete and distinct, and they were all greenish black. There was no bile retention in the liver, and aside from fluid blood in the general peritoneal cavity, there were no noteworthy abnormalities. The thorax, the neck, the floor of the mouth and the brain were not removed for examination.

CONCLUSION

This condition might be suspected in the presence of an enlarging tumor of the right upper part of the abdomen in a young female patient with jaundice. The condition, however, does occur in young male patients and middle-aged persons of both sexes and may not be associated with jaundice. The surgical treatment should depend on the findings in the individual case. The literature emphasizes the high mortality rate associated with aspiration alone or excision. Immediate anastomosis with the gastrointestinal tract may be indicated if the cyst is not too large, its identification is positive, and the patient's condition permits of such a procedure. The ill effects of the total absence of bile from the gastrointestinal tract when complete biliary fistula is established by marsupialization can now be partly obviated by the administration of vitamin K and bile salts or desiccated animal bile. Case 1 is the first to be recorded in which treatment with these agents has been carried out. Each of these cases provides an opportunity for the study of human fat absorption in the absence of bile from the gastrointestinal tract. When such a case is encountered, an immediate recourse to the literature is recommended for the recognition and the pursuit of the problems pertinent to this condition. The literature is so lacking in follow-up reports that the late results of anastomosis of these cysts with the gastrointestinal tract are unknown. Those who have performed operation in such cases are urged to report the late follow-up result of their cases.

622 West One Hundred and Sixty-Eighth Street.

BIBLIOGRAPHY

Adam, L.: Zentralbl. f. Chir. **50**:997, 1923.
Adeney, G. C.: Brit. M. J. **2**:415, 1923.
Akamine, K.: Nippon-Gekagakkai-Zassi **33**:598, 1932-1933.
Akiya, Y.: Nippon-Gekagakkai-Zassi **27**:1848, 1926-1927.
Arnison, cited by Mayo-Robson, 1904, p. 200.

Arnolds: Deutsche med. Wchnschr. **32**:1804, 1906.
Ashby, H.: M. Chron. **10**:28, 1898.
Backer-Grøndahl, N.: Med. rev., Bergen **50**:337, 1933.
Bakēs: Wien. klin. Wchnschr. **20**:298, 1907.
Barlach: Deutsche med. Wchnschr. **31**:369, 1877.
Bashkiroff, A. F.: Khir. Arkh. Velyaminova **27**:63, 1911.
Bazy, P.: Bull. Acad. de méd. **75**:137, 1916.
Bencčvić, J.: Liječn. vjesnik, 1928, vol. 6; abstracted, Zentralbl. f. Chir. **56**:1661, 1929.
Beneke, R.: Die Entstehung der kongenitalen Atresie der grossen Gallengänge nebst Bemerkungen über den Begriff der Abschnürung, Marburg, N. G. Elwert, 1907.
Bevan, A. D.: S. Clin. North America **2**:725, 1922.
Bistroff, P. V.: Kharkov. M. J. **19**:319, 1915.
Boehm, F.: Ztschr. f. ang. Anat. **1**:105, 1914.
Bohmansson, G.: Acta chir. Scandinav. **56**:440, 1924.
Bolle, H.: Deutsche med. Wchnschr. **48**:1381, 1922.
Bolling, R. W.: Ann. Surg. **79**:147, 1924.
Broca: Bull. et mém. Soc. de chir. de Paris **23**:209, 1897.
Brun: Bull. et mém. Soc. de chir. de Paris **23**:207, 1897.
Budde, M.: Deutsche Ztschr. f. Chir. **157**:364, 1920; **185**:339, 1924; Virchows Arch. f. path. Anat. **252**:442, 1924.
Butters: Deutsche med. Wchnschr. **36**:1351, 1910.
Buzik, J.: Arch. f. Verdauungskr. **23**:370, 1916.
Calcavara, E.: Virchows Arch. f. path. Anat. **141**:221, 1896.
Carr, G. L.: M. Woman's J. **47**:301, 1940.
Clairmont, P.: Wien. klin. Wchnschr. **24**:1616, 1911.
Clark, J. H.: Internat. Clin. **1**:78, 1932.
Davidson, P.: Liverpool Med.-Chir. J. **4**:226, 1884.
Derwissieu, A. A.: Zentralbl. f. Chir. **54**:852, 1927.
Descamps, P.: Bull. et mém. Soc. anat. de Paris **85**:328, 1910.
Djørup, F.: Zentralbl. f. Chir. **61**:428, 1934.
Douglas, H.: Monthly J. M. Sc. **14**:97, 1852.
Dreesmann: Deutsche Ztschr. f. Chir. **92**:401, 1908.
Duff, D. G.: Brit. J. Surg. **21**:536, 1934.
Ebner, A.: Beitr. z. klin. Chir. **64**:472, 1909.
Edgeworth, F. H.: Lancet **1**:1880, 1895.
Elischer, E.: Zentralbl. f. Chir. **50**:341, 1923.
Eljasberg, M.: Polska gaz. lek. **42**:617, 1924.
Elperin, S.: Frankfurt. Ztschr. f. Path. **12**:25, 1913.
Erdély, J.: Deutsche Ztschr. f. Chir. **209**:65, 1928.
Eve, F.: Brit. M. J. **1**:802, 1906.
Exner, A.: Wien. klin. Wchnschr. **24**:1615, 1911; **25**:469, 1912.
Fenger, C.: Tr. Am. S. A. **14**:699, 1896.
Feyrter, F.: Virchows Arch. f. path. Anat. **271**:20, 1929.
Fischel, A.: Lehrbuch der Entwicklung des Menschen, Berlin, Julius Springer, 1929.
Flechtenmacher, C.: Wien. klin. Wchnschr. **32**:365, 1919.
Fowler, R. S.: Ann. Surg. **64**:546, 1916.
Frerichs, F. T.: Pathologisch-anatomischer Atlas zur Klinik der Leberkrankheiten, Brunswick, Germany, F. Vieweg u. Sohn, 1861.
Frizelle, E. R.: Brit. M. J. **1**:610, 1932.

Fukamati, R.: Tokyo-Idi-Sinsi **1**:335, 1925.
Fukuda, T.: Nippon-Syokakibyogakkai-Zassi **21**:9, 1922.
Ghon, A., in Aschoff, L.: Pathologische Anatomie, ed. 7, Jena, Gustav Fischer, 1928, vol. 2, p. 857.
Giezendanner, E.: Frankfurt. Ztschr. f. Path. **38**:150, 1929.
Goldammer: Beitr. z. klin. Chir. **55**:214, 1907.
Hall, A. J.: Proc. Roy. Soc. Med. **16**:6, 1913.
Hamilton, I.: M. J. Australia **1**:800, 1939.
Hanser, R., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 5, pt. 2, p. 748; 1930, vol. 5, pt. 1, p. 42.
Hayasi, T.: Tyuagai-Idi-Simpo, 1920, no. 969, p. 934.
Heid, L.: Ein Fall von hochgradiger kystenartiger Erweiterung des Ductus choledochus, Inaug. Dissert., Giessen, 1893; cited by McWhorter.
Heidecker: Zentralbl. f. Chir. **55**:610, 1928.
Heiliger, J.: Ueber die congenitale cystenartige Erweiterung des Ductus choledochus, Med. Dissert., Giessen, O. Kindt, 1910.
Hertwig, O.: Die Elemente der Entwicklungslehre des Menschen und der Wirbeltiere, Jena, Gustav Fischer, 1920.
Hildebrand: Deutsche med. Wchnschr. **45**:2214, 1913.
Hill, N. H., and Ramsay, R. A.: Brit. M. J. **2**:991, 1925.
Huber, P., and Lutterotti, O.: Virchows Arch. f. path. Anat. **270**:243, 1928.
Idumi, G.: Dikken-Iho **9**:725, 1923.
Imai, T.: Tohoku-Igaku-Zassi **17**:99, 1934.
Ipsen, J.: Hospitalstid. **45**:1342, 1913.
Isawa, T.: Nippon-Gekagakkai-Zassi **30**:434, 1929-1930.
Iselin, H.: Arch. f. klin. Chir. **145**:304, 1927.
Isii, K.: Nippon-Gekagakkai-Zassi **22**:494, 1921-1922.
Isimaru, S.: Nippon-Gekagakkai-Zassi **31**:617, 1930-1931.
Isoda, S., and Kamida, U.: Nika-Zassi **390**:2189, 1932.
Ito, H.: Rinsyo-Igaku **8**:149, 1920.
Janik, A.: Chir. Klin. **2**:104, 1929.
Jauregui, P.: Rev. de cir. de Buenos Aires **7**:536, 1928.
Judd, E. S., and Greene, E. I.: Surg., Gynec. & Obst. **46**:317, 1928.
Kadikawa, T.: Idi-Simbun, 1930, no. 1263, p. 1034.
Kaira, K.: Kyoto-Idi-Eisei-Si **164**:4, 1907.
Kambe, V.: Arch. f. japan. Chir. **7**:74, 1930.
Kamiya, M.: Nippon-Gekagakkai-Zassi **32**:1494, 1931-1932.
Karell, U.: Esti Arst **10**:353, 1931.
Kasiwazaki, A.: Syonika-Zassi **1**:45, 1927.
Kato, K.: Rinsyo-Igaku-Syasin-Dufu, 1928-1930, vol. 8.
Kato, R.: Therapie **5**:632, 1928.
——and Igarasi, S.: Arch. f. japan. Chir. **5**:187, 1928.
Kawaisi, K.: Nippon-Gekagakkai-Zassi **23**:1171, 1922-1923; Aiti-Igakkai-Zassi **27**:1622, 1926-1927.
Kehr, H., in von Bruns, P.: Neue deutsche Chirurgie, Stuttgart, Ferdinand Enke, 1913, no. 8.
Kiselev, N.: Vestnik khir. **78**:182, 1932.
Kodumi, K., and Kodama, T.: Tokyo-Igakkai-Zassi **30**:1413, 1916.
Körte: Med. Praxis **4**:117, 1928.
Kolb, O.: Ein Fall von hochgradiger kystenartiger Erweiterung des Ductus hepaticus und des Ductus choledochus, Inaug. Dissert., Munich, 1906; cited by McWhorter.

Konitsky, G.: Ein Fall von hochgradiger cystischer Erweiterung der Ductus choledochus, Inaug. Dissert., Marburg, G. Schirling, 1888.
Konjetzny, G. E.: Ergebn. d. allg. Path. u. path. Anat. **14**:840, 1910.
Krabbel, M.: Beitr. z. klin. Chir. **130**:159, 1923.
Kremer, J.: Arch. f. klin. Chir. **113**:99, 1920.
Kulakoff, A. N.: Chir. sborn., 1924, p. 265.
Kuriyama, S.: Nika-Zassi **304**:1519, 1925; **376**:1334, 1931; **402**:2063, 1933; **404**: 101, 1934.
Kuru, S.: Rinsoyo-Igaku **1**:342, 1913.
Lange, K.: Zentralbl. f. Chir. **54**:2287, 1927.
Lavenson, R. S.: Proc. Path. Soc. Philadelphia **12**:73, 1908-1909; Am. J. M. Sc. **137**:563, 1909.
Legg, J. W.: Lancet **1**:190, 1877.
Letulle, M.: Presse méd. **21**:97, 1913.
Lindqvist, S.: Upsala läkaref. förh. **17**:271, 1911-1912.
McConnell, A. A.: Brit. J. Surg. **7**:520, 1920.
McWhorter, G. L.: Congenital Cystic Dilatation of Common Bile Duct, Arch. Surg. **9**:604 (March) 1924.
Masson, J. C., and Rieniets, J. H.: S. Clin. North America **2**:743, 1931.
Mathieu, P.: Rev. de chir. **27**:61 and 174, 1908.
Matthieu, J.: Ann. Surg. **92**:159, 1930.
Matida, T.: Nippon-Gekagakkai-Zassi **27**:1622, 1926-1927.
Mayesima, J.: Nippon-Gekagakkai-Zassi **12**:109, 1911-1912; Deutsche Ztschr. f. Chir. **119**:338, 1912.
Mayo-Robson, A. W.: Diseases of the Gall Bladder and Bile Ducts, ed. 3, New York, William Wood & Company, 1904; Lancet **1**:1529, 1897.
Melikhov, P. G.: Russk. klin. **3**:74, 1925.
Milner, S. W.: Brit. M. J. **1**:1235, 1909.
Mintz, W.: Zentralbl. f. Chir. **40**:1263, 1913.
Morinaga, K., and Atumi, R.: Nagasaki Igakkai Zassi **16**:251, 1938.
Morley, J.: Brit. J. Surg. **10**:413, 1922-1923.
Moynihan, B. G. A.: Brit. M. J. **2**:1390, 1905.
Nagayo, M.: Tokyo-Igakkai-Zassi **20**:669, 1906.
Nakamura, M.; Igarasi, H., and Fukusima, S.: Jap. J. Gastroenterol. **10**:670, 1935.
Narabayashi, T.: Zentralorg. f. d. ges. Chir. u. Grenzgeb. **25**:401, 1924; J. Orient. Med. **1**:122 and 316, 1923.
di Natale, L.: Arch. ital. di chir. **23**:553, 1929.
Neugebauer, F.: Beitr. z. klin. Chir. **131**:448, 1924.
Nicolaysen, J.: Nord. med. ark. **16**:1, 1899.
Nisizawa, T.: Nika-Zassi **78**:759, 1906.
Nogasaki: Igakkai Zassi **15**:251, 1928.
Ogata, T.: Beitr. z. path. Anat. u. z. allg. Path. **55**:236, 1913.
Ogawa, S.: Nika-Zassi **372**:715, 1931.
Oglobin, A. A.: Vestnik khir. **9**:177, 1927; abstracted, Zentralbl. f. Chir. **55**:33, 1928.
O'Gorman, F. M.; Chely, L., and Heyden, C. F.: New York State J. Med. **31**: 1196, 1931.
Okuya, H.: Grenzgebiet **2**:813, 1928.
Olivecrona, H.: Acta chir. Scandinav. **62**:347, 1927.
Outerbridge, G. A.: Proc. Path. Soc. Philadelphia **14**:174, 1912.
Oxley, M. G. B.: Lancet **2**:988, 1883.
Pamperl, R.: Med. Klin. **21**:1608, 1925.

Parker, G.: Lancet **2**:520, 1901.
Pellegrini, R.: Pathologica **6**:764, 1913.
Pfuhl, W., in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1932, vol. 5, pp. 235 and 426.
Popović, B.: Med. pregl. **4**:194, 1929.
de Quervain, F.: Spezielle chirurgische Diagnostik, ed. 8, Leipzig, F. C. W. Vogel, 1922, p. 398.
Raynaud, M., and Sabourin, C.: Arch. de physiol. **6**:37, 1879.
Reel, P. J., and Burrell, N. E.: Ann. Surg. **75**:191, 1922.
Reynier: Bull. et mém. Soc. de chir. de Paris **18**:803, 1892.
Rietz, J.: Nord. med. ark. **50**:1, 1917.
Roberts, E. D.: Un cas de dilatation kystique du canal cholédoque, Thesis, Lausanne, 1914.
Rolleston, H. D.: Diseases of the Liver, Gall Bladder and Bile Ducts, New York, The Macmillan Company, 1905.
Rosenberg, G.: Arch. f. klin. Chir. **125**:1, 1929.
Rostowzew, M. J.: Deutsche med. Wchnschr. **28**:739 and 758, 1902.
Rotgans, J.: Nederl. tijdschr. v. geneesk. **49**:1345, 1913.
Russell, R. H.: Ann. Surg. **26**:692, 1897.
Saint, J. H.: Brit. M. J. **1**:230, 1932.
Sakuma, S.: Okayama-Igakkai-Zassi **181**:49, 1905.
Santruček, K.: Časop. lék. česk. **71**:1185, 1932; abstracted, Zentralorg. f. d. ges. Chir. u. Grenzgeb. **60**:840, 1933.
Sato, M.: Okayama-Igakkai-Zassi **443**:1332 and 1348, 1926.
Sato, T.: Nippon-Gekagakkai-Zassi **21**:1, 1920-1921.
Savy, P.; Bonnet, P., and Martin, J. F.: Lyon chir. **9**:673, 1913.
Schloessmann: Deutsche Ztschr. f. Chir. **109**:160, 1911.
Schürholz: Arch. f. klin. Chir. **9**:118, 1921.
Schwalbe, E.: Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, Gustav Fischer, 1906.
Sebek, A.: Časop. lék. česk. **66**:1720, 1927; abstracted, Zentralbl. f. Chir. **54**:878, 1927.
Seeliger, S.: Beitr. z. klin. Chir. **99**:158, 1916.
Sekiguti, S.: Nippon-Gekagakkai-Zassi **13**:117, 1912-1913.
Sénèque, J., and Tailhefer, A.: J. de chir. **33**:154, 1929.
Seyffert, R. E.: Zur Pathologie der Gallengänge. Cyste des Ductus choledochus, operativ Behandelt, Inaug. Dissert., Greifswald, C. Sell, 1888.
Sieber, F.: Zentralbl. f. Gynäk. **53**:2848, 1929.
Simmonds: München. med. Wchnschr. **55**:2565, 1908.
Sioda, H.: Nippon-Gekagakkai-Zassi **13**:117, 1912-1913.
Sippel, P.: Med. Klin. **14**:504, 1918.
Skormin, B.: Jahrb. f. Kinderh. **56**:176, 1902.
Smit: Med. rev., Bergen **32**:285, 1915.
Söderlund, G.: Acta chir. Scandinav. **59**:253, 1925.
Sprengel: Ber. ü. d. Verhandl. d. deutsch. Gesellsch. f. Chir. **20**:132, 1891.
Stein, J.: Prag. med. Wchnschr. **35**:383, 1910.
Sternberg, C.: Wien. klin. Wchnschr. **23**:1616, 1911.
Stimson, P. M.: New York State J. Med. **23**:408, 1923.
Stoney, R. A.: Irish J. M. Sc., 1929, p. 764.
Sugaya, T.: Seikai-Geppo **434**:168, 1918.
Sumpter, W. D.: South. Practitioner **39**:169, 1917.

Swain, W. P.: Lancet **1**:743, 1895.
Tailhefer, A.: Bull. et mém. Soc. nat. de chir. **60**:8, 1934.
Takaisi, D.: Osaka-Igakkai-Zassi **13**:935, 1914.
Tanaka, K.: Rinsyo-Igaku **12**:949, 1924.
Taylor, J.: Brit. J. Surg. **16**:327, 1928.
Terada, H., and Yagi, Y.: Nika-Zassi **367**:2078, 1930.
Terrier, F.: Rev. de chir. **13**:81, 1893.
Todd, C. H.: Dublin Hosp. Rep. **1**:328, 1817.
Towara, M.: Nika-Zassi **370**:480, 1931.
Tudimura, H.: Arch. f. japan. Chir. **4**:799, 1927.
Ugelli, L.: Policlinico (sez. chir.) **40**:343, 1933; abstracted, Zentralorg. f. d. ges. Chir. u. Grenzgeb. **63**:651, 1933.
Utida, T.: Tokyo-Idi-Sinsi **55**:2550, 1931.
Vater, A.: Diss. anatomica qua novum bilis diverticulum circa orificium ductus choledochi . . . Wittenberg, lit. Gerdesiams, 1720.
Diss. Regiae Magnae Britanniae Societati dicata, Wittenberg, sumpt. viduae Gerdesiae, 1723.
Veau, V.: Presse méd. **18**:495, 1910.
Wagner, A.: Deutsche Ztschr. f. Chir. **145**:15, 1918.
Waller, E.: Ann. Surg. **66**:446, 1917.
Walters, W.: Personal communication to the author.
Walzel, P., and Weltmann, O.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **37**:437, 1924.
Watanabe, H.: Nippon-Gekagakkai-Zassi **29**:416, 1928-1929.
Weeder, S. D.: Ann. Surg. **110**:55, 1939.
Weiss, S.: Berl. klin. Wchnschr. **46**:1843, 1909.
von der Weth, G.: Jahrb. f. Kinderh. **97**:259, 1922.
Wettwer, E.: Ein Fall von kongenitalen Choledochuscyste, Inaug. Dissert., Göttingen, W. F. Kaestner, 1907; cited by Waller.
Wickham, L. J.: Tr. Path. Soc. London **27**:178, 1875.
Wilks, S., and Moxon, W.: Lectures on Pathological Anatomy, ed. 3, London. Longmans, Green & Company, 1889, p. 485.
Willis, B. C.: Ann. Surg. **87**:48, 1928.
Wilson, H. V., Jr.: Choledochus Cyst: Report of Case, J. A. M. A. **95**:399 (Aug. 9) 1930.
Winterstein, O.: Wien. med. Wchnschr. **82**:638, 1932.
Witzel, O.: Zentralbl. f. Gynaek. **4**:561, 1880.
Wright, H. W. S.: Surg., Gynec. & Obst. **39**:156, 1924.
Wyllie, W. G.: Lancet **1**:1342, 1925.
Yagi, Y.: Nika-Zassi **340**:1635, 1928.
Yamanouchi, K.: Ztschr. f. japan. chir. Gesellsch. **22**:1921; Zentralorg. f. d. ges. Chir. u. Grenzgeb. **16**:228, 1922.
Yamanouti, T.: Nippon-Gekagakkai-Zassi **22**:373, 1921-1922.
Yasui, K.: Nika-Zassi **247**:1057, 1920.
Ylppó, A.: Ztschr. f. Kinderh. **9**:319, 1913.
Yotuyanagi, S.: Jap. J. Cancer Research **30**:601, 1936.
Young, R. F.: Glasgow M. J. **108**:346, 1927.
Zaczek, J. K.: Polski przegl. chir. **6**:639, 1927; abstracted, Zentralbl. f. Chir. **56**:242, 1929.
Zimmer, H.: Zentralbl. f. Chir. **51**:424, 1924.
Zinninger, M. M., and Cash, J. R.: Congenital Cystic Dilatation of the Common Bile Duct, Arch. Surg. **24**:77 (Jan.) 1932.
Zipf, K.: Arch. f. klin. Chir. **122**:615, 1923.

ABSORPTION OF SURGICAL GUT (CATGUT)

II. PEPSIN DIGESTION TESTS FOR EVALUATION OF DURATION OF TENSILE STRENGTH IN THE TISSUES

HILGER PERRY JENKINS, M.D.
AND
LEO S. HRDINA
CHICAGO

The decline in tensile strength of various sizes, types and brands of surgical gut (catgut) in the tissues was reported in a previous communication.[1] A considerable amount of variation was generally observed in the behavior of the different products studied. This report deals with digestion tests in pepsin and the relation of the digestion time in pepsin to the duration of tensile strength of catgut in the tissues.

Kraissl and Meleney [2] reported an ingenious method of assaying the resistance of catgut by trypsin digestion in vitro. The end point, at which the catgut undergoes complete loss of tensile strength in the digestive solution, is recorded by means of an electric clock. The electric current to the clock is shut off by means of a switch which is thrown by a counterweight when the catgut strand breaks. The digestion time in hours can then be determined from the time the test was started to the time when the clock was shut off.

It is presumed that all manufacturers of surgical gut have some type of digestion test in vitro which is used in attempting to control the absorption time of their products. It is probable that trypsin is the most generally used enzyme for this purpose. Since the publication of the work by Kraissl and Meleney and a subsequent paper by Kraissl,[3] several manufacturers have utilized this method or a modification thereof.

From the Department of Surgery, the University of Chicago, the School of Medicine.

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1. Jenkins, H. P., and Hrdina, L. S.: Absorption of Surgical Gut (Catgut): I. Decline in Tensile Strength in the Tissues, Arch. Surg. **44**:881 (May) 1942.

2. Kraissl, C. J., and Meleney, F. L.: A Method for Determining the Time of Catgut Digestion in Vitro, Surg., Gynec. & Obst. **59**:161, 1934.

3. Kraissl, C. J.: Intrinsic Factors Altering the Absorption of Catgut, Surg., Gynec. & Obst. **63**:561, 1936.

It is of interest to note that Claudius [4] in 1912 reported the use of pepsin and hydrochloric acid in an attempt to evaluate the absorbability of different kinds of catgut.

Because of the unpredictable behavior in the tissues of different sorts of surgical gut, notwithstanding the rather specific labels customarily used by manufacturers in the past, there appeared to be a place for further work in the field of digestion tests for catgut. Rather than pursue a course which was already being followed by Kraissl and Meleney in their trypsin digestion tests, it appeared desirable to explore the possibilities of another enzyme, such as pepsin, to ascertain whether this might offer a satisfactory basis for evaluating the absorption qualities of surgical gut.

METHODS AND MATERIALS

30 Gm. Tension Pepsin Digestion Test.—After the apparatus designed by Kraissl and Meleney for their trypsin digestion test of catgut in vitro had been inspected, a similar type of apparatus was devised. This consisted of a small incubator in the top of which several holes were bored. A large glass jar to contain the digestive solution was placed in the incubator. The catgut strands were tied to a glass rod above the jar and then carried down into the jar, where they were held in the solution by passing under another glass rod. From there the catgut strands extended upward through one of the holes in the top of the incubator to be attached by a clasp to a cord running over two pulleys to a 30 Gm. lead weight. This weight maintained a constant tension on the catgut, and when the catgut became digested and broke, the lead weight disconnected an electric switch which controlled the circuit to an electric clock. The apparatus so devised accommodated twelve strands of catgut at one time, each of which was fastened to a cord which broke the circuit to one of the twelve electric clocks. The time at which the clock had been stopped represented the end point of the digestion test for that particular strand of catgut. It was necessary to make observations each night in addition to observations during the day, because if the clock stopped at 7:30 one would not otherwise know whether it was 7:30 a. m. or 7:30 p. m. Kraissl solved this point by installing a set of electric clocks with twenty-four hour dials in his more recent digestion apparatus.

The digestive solution originally used for a limited number of tests was pure gastric juice obtained from dogs. Large quantities of this juice were available because of an experimental study of gastric secretion by Dragstedt and associates.[5] The desirability of an artificially prepared standard strength solution soon became obvious because of the variations in the digestive action of the different supplies of this gastric juice. Experiments were conducted to ascertain what concentrations of pepsin and hydrochloric acid most nearly approximated the results obtained with pure gastric juice. It was found that 10 Gm. of pepsin (U. S. P.) and 1 cc. of concentrated hydrochloric acid made up to 100 cc. with water gave results most comparable with those obtained by the use of the pure gastric juice. The tem-

4. Claudius, M.: Jodchromkatgut, Deutsche med. Wchnschr. **38**:1050, 1912.

5. Dragstedt, L. R., and Ellis, J. C.: The Fatal Effect of the Total Loss of Gastric Juice, Am. J. Physiol. **93**:407, 1930.

perature of the incubator was maintained at 37 C. Over 1,200 digestion tests were carried out with this acid-pepsin mixture and the apparatus described.

2 Gm. Suspension Pepsin Digestion Test.—A relatively simple method of testing catgut in vitro was devised which presented certain advantages over the more elaborate method requiring the use of electric clocks. A standard 100 cc. glass cylindric graduate 9½ inches (24 cm.) in height and 1 inch (2.5 cm.) in diameter was used. A small split lead shot, such as one uses on a fishing line, was attached to one end of a 10 inch (25.4 cm.) length of catgut by forcefully closing the split shot on the catgut strand. The weight of this lead shot was approximately 2 Gm. The catgut strand was lowered into the glass cylinder until the top of the lead shot was at a level with the 10 cc. mark on the graduate. The upper end of the catgut was fastened to the neck of the glass cylinder by a strip of adhesive tape. The digestive solution was warmed to body temperature and poured into the glass container, 110 cc. of solution being used. Any shrinkage of the catgut could then be measured in terms of percentage of the original length submerged in the solution by reading from the graduate the level of the lead shot as compared with its original level at the 10 cc. mark. For example, if the lead shot was sighted at the 30 cc. mark on the graduate after several hours in the solution this represented 20 per cent shrinkage. Observations of shrinkage and subsequent stretching of the catgut during the course of digestion were considered important aspects of the test. The end point was considered to be the time when the catgut was sufficiently digested to break and permit the lead shot to drop to the bottom of the glass. The digestion time in hours was computed from the time the test was started in the incubator until the catgut broke. Four or five strands of catgut were usually placed in one cylinder. It was necessary to use some means of holding the catgut strands away from the glass at the surface level of the digestive solution. This was usually done by a heavy malleable wire which fitted snugly within the neck of the glass graduate above the level of the solution.

The digestive solution used was the same as that mentioned for the 30 Gm. test, i. e., 10 per cent (by weight) pepsin and 0.35 to 0.37 per cent hydrochloric acid (1 cc. concentrated hydrochloric acid to 100 cc. of solution). Readings were made at half-hour to one hour intervals on plain catgut and one to four hour intervals on chromic catgut, depending on the particular product being tested and the stage of digestion. The level of the lead shot attached to each strand was read from the scale on the graduate and recorded so that one would know whether the catgut was undergoing shrinkage or stretching by comparing the data of this observation with previous observations. If one was in the room in which the incubator was installed, one could often detect the sound of the lead weight striking the bottom of the glass as the catgut broke. Many end points were thus accurately recorded. Otherwise the end points were considered to be halfway between the time of the last intact observation and the time when the catgut was found to be broken. It was often necessary to watch these digestion tests throughout the night, although, after becoming familiar with the behavior of the various brands of catgut one could start the tests at a time which permitted observation of the end points at more convenient times. In some instances the glass graduates were placed in an ice box overnight and then replaced in the incubator the following morning. The time spent in the ice box was of course not included in the digestion time recorded for the catgut. This relatively simple method permitted carrying out as many as 100 catgut digestion tests at one time in an ordinary laboratory incubator. The thermostat was set for 37 C. For these tests an incubator with inner glass doors

was used, so that the observations could be made without appreciably disturbing the temperature within the incubator. Approximately 2,000 digestion tests were carried out by this method.

Catgut Tested.—The standard surgical gut of ten different manufacturers was subjected to pepsin digestion tests in vitro. The surgical gut used in these tests was essentially the same as that utilized for tissue implants described in the previous communication. The series of 1937, 1938 and 1939-1940 represent work carried out for the most part during those years on catgut obtained about that time. In the series of 1939-1940, a portion of the same strand of surgical gut used for duplicate tissue implants was subjected to duplicate 2 Gm. suspension digestion tests in pepsin. In the series of 1938, surgical gut obtained from the same lots as those used for tissue implants was checked by the 2 Gm. suspension test. In the series of 1937, the 30 Gm. tension pepsin digestion test was used on surgical gut of similar lots and also on portions of the same strands employed for tissue implants.

The plain, the twenty day or medium chromic and the forty day or extra hard chromic catgut of six manufacturers were tested in sizes from no. 2 to no. 000. This included one product labeled tanned instead of chromic catgut. The twenty day chromic catgut in sizes no. 2, no. 0 and no. 000 of four other companies also was tested. A number of samples of raw unsterilized catgut obtained from several sources were subjected to pepsin digestion. To avoid any misunderstanding regarding the terminology of catgut, it is advisable to review the present method of labeling different types of surgical gut officially adopted by the Committee of Revision of the United States Pharmacopeia.

Official U. S. P. Terminology	Presumably Equivalent Terminology Formerly in Use
Type A: Plain surgical gut (untreated)	Plain catgut
Type B: Mild chromic surgical gut (mild treatment)	Ten day chromic catgut
Type C: Medium chromic surgical gut (medium treatment)	Twenty day chromic catgut; medium hard chromic catgut, ten to twenty day
Type D: Extra chromic surgical gut (prolonged treatment)	Forty day chromic catgut; extra hard chromic catgut, thirty to forty day

The catgut was prepared for the digestion tests by softening in water until it was pliable and then hanging it up to dry with a 35 to 70 Gm. weight tied at one end. Particular care was taken to avoid fracturing the brittle bends in the dry catgut or causing any mechanical damage to the strand. This point has been mentioned by Kraissl as a possible factor in the explanation of discrepancies in digestion tests in trypsin. Even recently opened tubes of nonboilable catgut, which is reasonably pliable, were soaked in water to permit greater pliability before it was stretched out to dry. After the catgut was dry, determinations of the diameter and the tensile strength were made. The catgut was then cut into 10 inch (25.4 cm.) lengths for the 2 Gm. suspension test. Somewhat less than a half standard length of catgut was required for the 30 Gm. tension tests.

RESULTS

Behavior of Catgut in Acid-Pepsin Solution.—During the course of digestion in acid-pepsin solution by the 2 Gm. suspension method, catgut undergoes an original shrinkage phase, an intermediary stationary phase

and, finally, a stretching phase, which is terminated by the breaking of the digested strand. During the first part of the shrinkage phase there may be noticeable evidence of unwinding of the catgut strand, which causes the lead weights to spin around. This may lead to tangling of the several strands in the glass cylinder. Considerable attention is required at the beginning of the digestion test to avoid this difficulty.

The shrinkage observed is undoubtedly due to the acid medium, because comparable amounts of shrinkage occur in the same dilution of acid without the pepsin. The amount of shrinkage bears a relation to the size of the catgut strand, for the larger sizes usually shrink more than the smaller sizes of comparable type. The temperature of the digestive solution affects the magnitude of shrinkage, because in chilled solutions the shrinkage is considerably less. Heat-sterilized catgut undergoes much more shrinkage than the raw product which has not been subjected to heat sterilization.

The rate and the magnitude of shrinkage were found to bear a relation to the length of time required for digestion of the catgut. Those sutures which demonstrated a rapid and considerable shrinkage, of 15 to 30 per cent within an hour or two, were usually found to have a short digestion time, whereas the sutures which showed a slow rate and a lesser magnitude of shrinkage were digested in longer periods of time.

After the phase of shrinkage had gradually reached its maximum, there was a variable intermediary stationary phase before the onset of the stretching phase. The stretching phase undoubtedly represents advanced digestive action of the pepsin on the catgut. The breaking time of the catgut was nearly always during the stretching phase. If the break occurred before the onset of the stretching phase, it was usually found to be due to some local defect in the catgut which caused an apparently greater degree of vulnerability to digestion at this point than was observed for the rest of the strand. In some instances the break did not occur until the strand had regained its original length or had stretched even further. This was observed in some brands of rather thoroughly chromicized fine sutures.

In some of the earlier tests it was found that premature breaking would occur if the catgut strand rested against the side of the glass cylinder at the level of the digestive solution. This can be prevented by the device mentioned, i. e. placing a thick malleable wire ring within the neck of the glass cylinder. Occasionally the lead weights fell off the end of the strand if they had not been properly attached; however, this did not occur more than once in several hundred tests. It was exceedingly rare to find that the breaking point of the strand of catgut was near the place where the lead weight was attached.

When tests were carried out with the use of a small lead weight (2.5 to 5 Gm.) with a wire loop (fishing line sinker) to which the catgut was tied, it was found that plain catgut and certain types of chromic catgut became sufficiently altered by the acid-pepsin solution to cause spontaneous untying of the knots long before the catgut was digested. This untying phenomenon occurred regardless of the care taken in tying a triple throw square knot. This was observed also in pure gastric juice and in gastric contents siphoned from patients after gastrointestinal

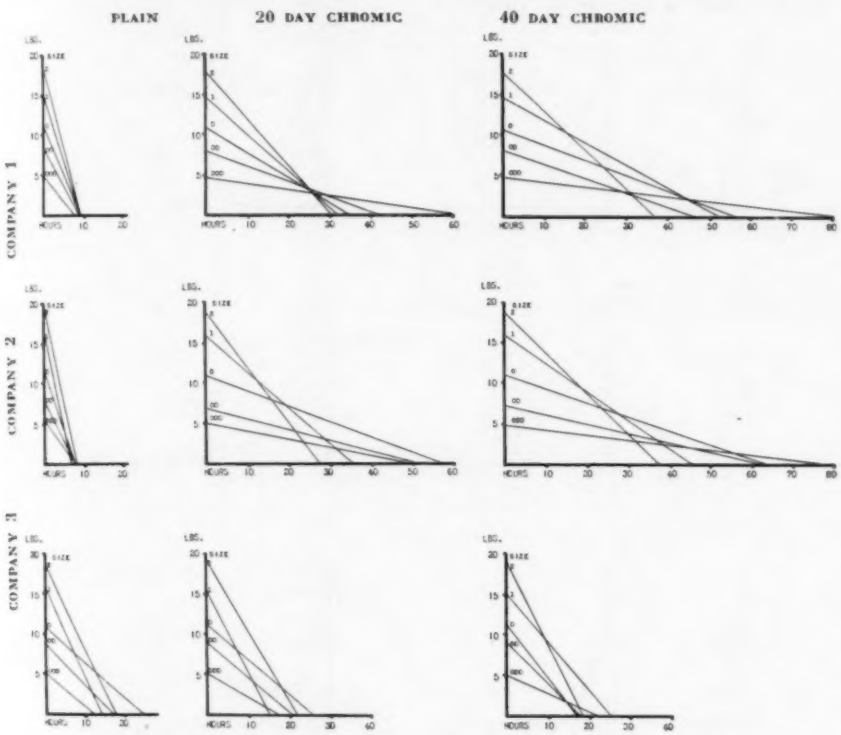

Fig. 1.—Charts showing digestion time of catgut in acid-pepsin solution (series 1939-1940).

anastomosis. The implication of this untying phenomenon in regard to the selection of surgical gut for gastrointestinal anastomosis should be obvious. However, the smaller sizes of the more resistant types of chromic catgut showed almost no tendency to untie spontaneously during the course of acid-pepsin digestion, and, furthermore, it was exceedingly unusual to find that the breaking point occurred at the knot, although it is well known that a knot weakens the tensile strength of catgut by an appreciable amount.

2 Gm. Suspension Pepsin Digestion Tests (figs. 1 to 5; series 1939-1940 and 1938).—In the 2 Gm. suspension pepsin digestion tests, plain catgut was digested within eleven hours on the average, although the digestion time in certain instances was as long as twenty hours or more. The larger sizes of plain catgut showed a tendency to resist digestion longer than smaller sizes, although frequent exceptions to this general tendency were observed.

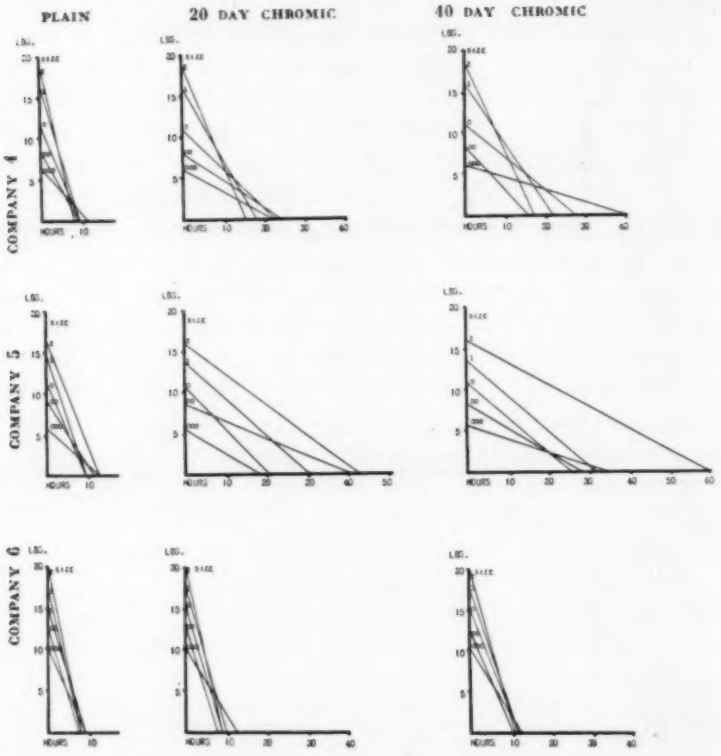

Fig. 2.—Charts showing digestion time of catgut in acid-pepsin solution (series 1939-1940).

The average digestion time of chromic catgut of different manufacturers varied widely. The digestion time of most of the products averaged more than twenty hours, although that for the products of two companies was almost the same as that generally observed for plain catgut. Differences between the twenty day chromic and the forty day chromic catgut of the same company and of the same size were of relatively minor magnitude as compared with the variation in the products of different companies.

In a considerable number of products there was a conspicuous tendency for the smaller sizes of chromic catgut to resist digestion longer than the larger sizes in both the twenty day and the forty day type of surgical gut. In other products the larger sizes frequently held

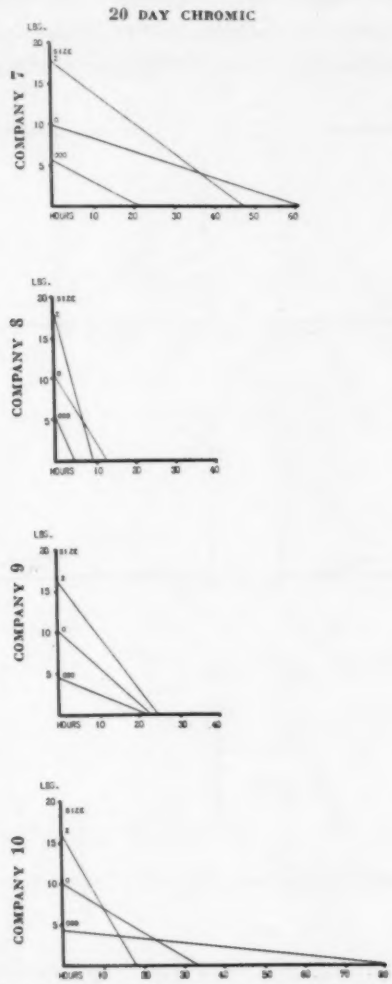

Fig. 3.—Charts showing digestion time of catgut in acid-pepsin solution (series 1939-1940).

up better than the smaller sizes, although in some instances it was difficult to ascertain any special trend in the behavior of the various sizes.

There was a considerable similarity in the behavior of any one product from year to year, although some appreciable differences were observed.

30 Gm. Tension Pepsin Digestion Test (fig. 6; series 1937).—In the 30 Gm. tension pepsin digestion tests, plain catgut was digested in twenty-five to fifty hours, and chromic gut was digested in fifty to one hundred and twenty-five hours or more. The conspicuously longer digestion time by this method was apparently due to maintaining the catgut at a constant tension of 30 Gm. instead of the 2 Gm. used for the suspension test. Experiments involving the use of different weights on

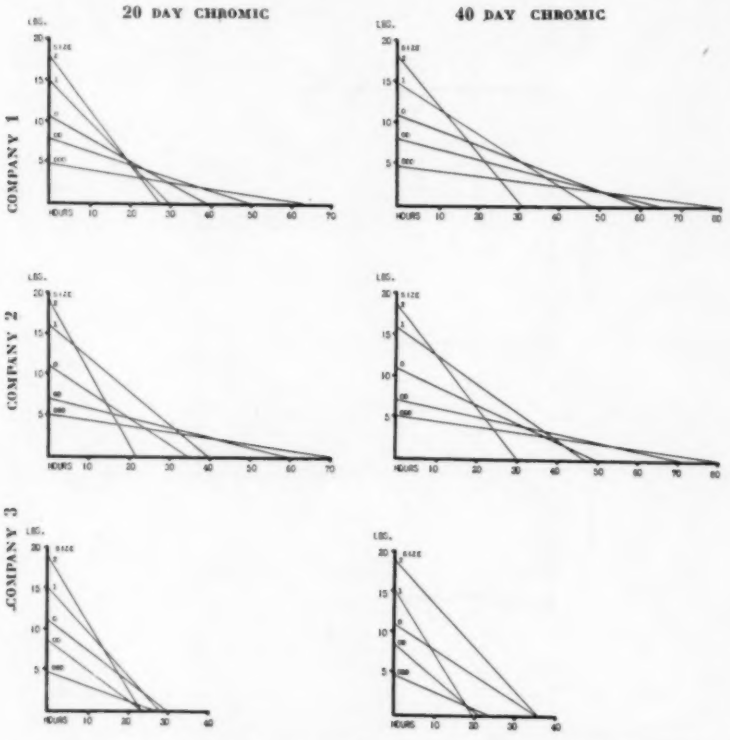

Fig. 4.—Charts showing digestion time of catgut in acid-pepsin solution (series 1938).

portions of the same strand of catgut suspended in the same solution demonstrated that the difference in digestion time was due to the difference in the degree of tension under which the catgut was subjected to the digestive solution rather than to any variation in the potency of the pepsin. The greater tension on the catgut strand subjected to pepsin digestion appeared to delay the penetration of the peptic ferment, and a longer digestion time was the result.

For purposes of comparison of the results obtained by the 30 Gm. tension tests and the 2 Gm. suspension tests, it was found that an approximate relation of $2\frac{1}{2}:1$ existed between the digestion times obtained by these two methods. The charts showing the digestion time in pepsin by the 30 Gm. tension test were made up in such a way that the unit for designating twenty-five hours by this method was the same as was used for indicating ten hours by the 2 Gm. suspension method.

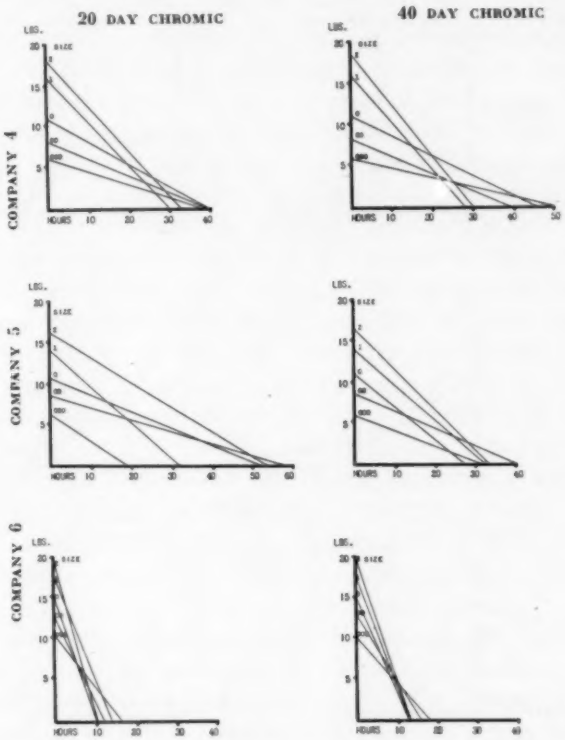

Fig. 5.—Charts showing digestion time of catgut in acid-pepsin solution (series 1938).

Thus fifty hours was equivalent to twenty hours by the 2 Gm. method, and one hundred hours was expressed by the same unit that designated forty hours by the latter test.

With this relation established, it will be found that the general pattern of behavior of the various kinds of surgical gut tested in the series of 1937 was to a considerable extent comparable to the observations made on the other series in which the 2 Gm. suspension method was used. There was, however, a tendency for the various types of

plain catgut to hold up slightly longer in the pepsin under 30 Gm. tension than might be expected if the ratio of $2\frac{1}{2}:1$ is an approximation of the relation in view of the observations generally made by the 2 Gm. tests in the series of 1939. On the other hand, it will be observed that the plain catgut in the series of 1937 may have been somewhat more resistant to digestion because of the slightly longer duration of tensile strength in the tissues observed for this series as compared with the 1939-1940 series.

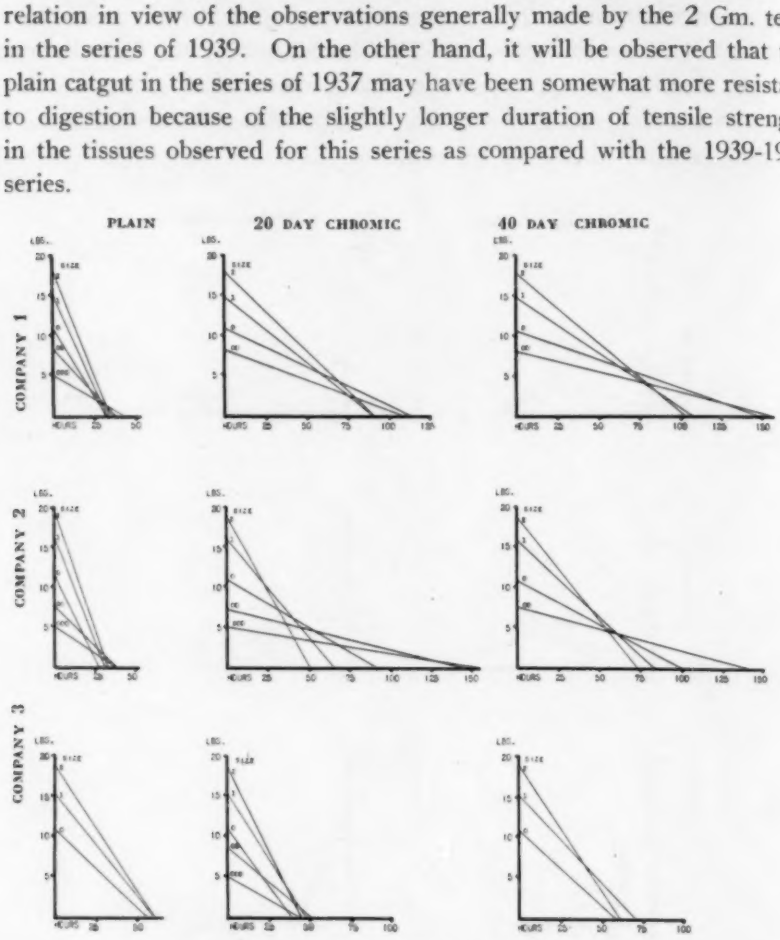

Fig. 6.—Charts showing digestion time of catgut in acid-pepsin solution (series 1937).

The shrinkage and the unwinding phenomena described previously were observed also in tests made with the 30 Gm. tension method but were of less magnitude than in the 2 Gm. suspension test. In some instances these phenomena caused difficulties in the digestion apparatus, which, however, could be easily remedied by attention to the apparatus during the earlier phases of the digestion tests.

Raw catgut which had not been heat sterilized was found to have a rather wide range of variation in digestion time in pepsin. Plain

unsterilized catgut was digested in three to ninety hours by the 30 Gm. tension method and in one and a quarter to thirty hours by the 2 Gm. suspension method, depending on the source from which it was obtained. Chromicized catgut which had not been heat sterilized was found to have a somewhat longer digestion time than was usually observed for the heat-sterilized product of that particular company.

RELATION OF DIGESTION TIME IN PEPSIN TO DURATION OF TENSILE STRENGTH IN THE TISSUES

The method of computing the relation between digestion time in pepsin and the duration of tensile strength in the tissues was as follows: The products of companies 1 to 6 were used for this comparison because these products represented the bulk of the observations made. The series of 1938 and 1939-1940 were taken because the 2 Gm. suspension method was used in these two series. The average digestion time of the plain catgut of all six companies was computed from 350 tests. The average digestion time of the chromic catgut of each of the six companies was determined from a total of 1,190 tests. The minimum number of tests entering into the average for any one company was not less than 150. The tests of twenty day chromic and forty day chromic catgut were averaged together. The various sizes of catgut from no. 2 to no. 000 were equally represented in the averages. The average duration of tensile strength as determined by implants in the abdominal muscles of dogs (reported previously) was computed for these same products. The average duration of the tensile strength of plain catgut was determined from 303 observations, while that for chromic catgut of each of the companies was made from a total of 925 implants. These digestion tests were made on portions of the same strand of catgut or on catgut from the same lots that were used for implants in the tissues.

When the results were plotted on a graph, using the vertical coordinates for digestion time in pepsin and the horizontal coordinates for the duration of tensile strength in the tissues, it was found that the various points were generally falling along a straight line except the point for the chromic catgut of company 2 (fig. 7). It is probable that the relation denoted in the graph is more of a curved line, as indicated on the graph by the interrupted line, because pepsin does undergo some deterioration in its digestive action during the course of the tests. However, for purposes of charting the results on digestion tests as compared with the duration of tensile strength in the tissues, the straight line relation will be considered a reasonable approximation of the situation. On this basis ten hours in digestion time will be considered as approximately equivalent to five days' duration of tensile strength in the tissues, or a ratio of two hours to one day.

The charts showing the digestion time in pepsin are made up in such a way that the unit for designating ten hours is the same as that used to designate five days' duration of tensile strength in the tissues in the charts presented previously. Further, the charts are arranged in the same sequence as those showing the results of implants in the tissues to facilitate comparison. In all these charts the vertical coordinates represent tensile strength in pounds. In this way it is possible to visualize the decline in tensile strength of the various sizes of catgut used. Also, one can then ascertain approximately the residual tensile strength of the catgut at any given time in pepsin or in the tissues. Although

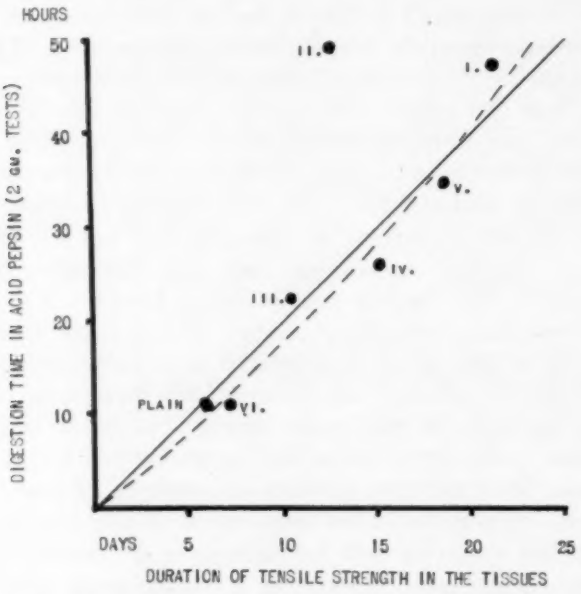

Fig. 7.—Graph showing relation between the digestion time in acid-pepsin solution and the duration of the tensile strength in the tissues of the surgical gut of six manufacturers (companies I to VI). The plain catgut of all companies has been averaged together; the chromic catgut of different companies has been averaged separately. The continuous line represents the approximate relation, i. e., ten hours in acid pepsin is equivalent to about five days in the tissues; the broken line represents the theoretic curve of relation.

the use of a straight line to denote graphically the decline in tensile strength of catgut in the tissues and in pepsin may be open to some criticism, it nevertheless offers a satisfactory method of comparing the relative behavior of the various products in the tissues and in pepsin.

In reviewing the various charts for the several series presented by comparing side to side the general behavior of catgut in pepsin and in

the tissues, the details of the general relationship can be more fully visualized. Although each size of every type of catgut of each of the companies in the three series studied is not invariably identical in its behavior in pepsin and in the tissues, there is nevertheless a comparable trend of behavior for the most part. In view of the fact that the previously reported tests conducted in the tissues are not considered to be more than gross evaluations of the duration of tensile strength, it is surprising to find as much similarity as apparently exists in the various sizes, types and brands of catgut compared.

On the basis of the digestion test one can with some degree of accuracy detect those products or particular sizes of certain products which did not hold up in the tissues for a period of ten days, even though they may have been labeled twenty or forty day catgut, because these usually had a digestion time which was less than twenty hours by the 2 Gm. suspension test. To maintain tensile strength for ten days in the tissues, a treated type (chromic or tanned) of surgical gut should have approximately twice the degree of resistance to digestion possessed by most brands of plain (untreated) catgut.

Also one can ascertain with reasonable accuracy which products have a relatively higher degree of resistance to tissue digestion in the smaller sizes of chromic catgut as compared with the larger sizes, because the digestion time in pepsin is conspicuously longer for the relatively more resistant smaller sizes.

A number of discrepancies of an appreciable magnitude, however, will be noted. In the series of 1939 the plain catgut of company 5 showed a greater resistance to tissue digestion than one would have presumed from the results of the pepsin tests. In the same series the plain catgut of company 3 demonstrated a greater resistance to pepsin digestion than was observed in the tissues. Furthermore, the observations on the chromic catgut of company 2 in all series tested showed a relatively higher degree of resistance to pepsin digestion than was observed in the tissues. In these instances the ratio of digestion time in pepsin as compared with duration of tensile strength in the tissues did not follow the general relationship established for most of the catgut studied which was expressed in the ratio of two hours to one day.

It is rather difficult to explain the discrepancies which have been noted. There are probably a number of factors to be considered, such as the management of the raw product, the duration and temperature of heat sterilization and the chemical agents in the tubing fluid, as well as details in the method of chromicizing. Most of these factors are obviously beyond the scope of the individual investigator, because to a considerable extent they represent trade secrets. Without recourse to practically every detail in the preparation and manufacture of surgical

gut, it is doubtful whether digestion tests in vitro can be considered completely reliable in ascertaining the expected duration of tensile strength in the tissues of all varieties of surgical gut.

One can speculate regarding some of the factors mentioned. A particular method of chromicizing may render catgut resistant to enzyme digestion in vitro, but because of some irritating substances in the chromic catgut which cause tissue reaction of appreciable magnitude, the rate of digestion in the tissues of this chromic catgut may become accelerated. The irritation may be the result of chemicals used in the tubing fluid, of chemicals which have not been adequately washed out of the catgut after the chromicizing process, or of so-called unfixed chromic compounds. Another possibility is that the products of digestion of this type of chromic catgut may be more irritating to the tissues than chromic catgut prepared by different methods. The presence of irritating substances may cause considerable tissue reaction with exudation and leukocytic infiltration. This increased tissue reaction could probably hasten the absorption of the catgut in the tissues. If a particular type of chromic catgut does cause more tissue reaction than other types of chromic catgut, it should not be surprising to find that its resistance to pepsin digestion does not bear the same relation to tissue absorption as chromic catgut prepared by other methods.

A factor which may enter into the explanation of the variability of results obtained by digestion tests from time to time on some products is that there may be a fundamental difference in the raw products used in the manufacture of chromic catgut. The wide range of variation in the digestion tests on several sources of raw plain unsterilized catgut indicates that there may be appreciable differences in the inherent resistance of the raw product. Furthermore, there may be differences in the response of various raw products to chromicizing. In spite of careful methods of chromicizing, it is amazing that manufacturers are able to produce a chromic catgut with as much precision as is usually done in view of the variable aspects of the original raw product. It is possible that considerable differences in the original raw product may be responsible for some of the differences in digestion time observed in the same companies' products from one year to the next, although changes in the chromicizing process also have to be considered.

COMMENT

A number of points must be taken into consideration in evaluating the reliability of a digestion test designed to assay the absorption qualities of surgical gut. In the first place, the digestive agent deserves consideration, because of the variation in the potency of commercial preparations of enzymes. In an attempt to minimize this factor, pepsin was

obtained from one source. For the series of 1939-1940, one large lot was obtained which was adequate for all the tests. Various lots of pepsin used throughout the earlier course of this work did not appear to vary in digestive rate by more than 10 per cent or possibly 15 per cent at the most. Whatever variation did occur from various lots of pepsin was fairly well distributed among the tests on assorted products, because no one product was continuously subjected to tests with a particular lot of pepsin.

The rate of deterioration of the digestive enzyme during the course of the digestion test should be considered. An attenuation of the digestive action due to prolonged incubation would give a longer digestion time than the actual resistance of the catgut would justify. It is probable that the exceedingly long digestion time observed for certain small sizes of chromic catgut was due to some extent to the gradual attenuation of the peptic action. A number of tests were conducted to ascertain whether the rate of peptic digestion was consistent throughout the time generally required to digest most products. Five portions of the same strand of catgut were incubated in the same solution. These were removed at various intervals and hung up to dry. The residual tensile strength was determined. The results were plotted on a graph, and it was found that the decline in tensile strength of catgut in pepsin was reasonably consistent during the first forty hours or so but that after this length of time there were some conflicting observations. It was observed, however, that as the catgut approached the end point of its digestion time there was a slight lag in the rate of digestion; this was denoted in the graphs by a tapering off of the relatively straight line as it approached the base line.

The use of relatively high concentrations of pepsin, such as 10 per cent, appears to minimize the attenuation of the digestive action of this enzyme. Also this concentration results in more rapid digestion than is observed with 2 per cent pepsin. Tests conducted with 2 per cent pepsin were approximately 25 per cent longer than those observed for 10 per cent pepsin when portions of the same strand of catgut were checked.

By using a small weight, such as 2 Gm., instead of 30 Gm. for maintaining tension on the catgut during digestion a considerably more rapid rate of digestion is accomplished. The heavier weight prolongs the digestion time by approximately two and a half times that observed with the smaller weight. This factor of a small weight undoubtedly favors the accuracy of the test by increasing the rate of digestion, thereby permitting the completion of the test on most products before any considerable amount of deterioration of the pepsin occurs.

Theoretic objections to the use of a lead weight suspended in an acid medium might be considered; however, the action of the dilute acid on

the lead was of such negligible magnitude that it appeared to have no practical importance as far as the reliability of the test was concerned.

In regard to the problem of preventing the digestive medium from becoming a culture medium for bacterial growth, as is usually observed in trypsin digestion tests carried on for any moderate length of time without the use of a bacteriostatic agent, it was found that the concentration of acid in the acid-pepsin solution was adequate to prevent any apparent difficulties from the growth of organisms.

Certain features of the 2 Gm. suspension pepsin digestion test appear to increase its reliability over that of a test in which the end point is the only observation made. The rate and magnitude of shrinkage, the duration of the intermediary stationary phase and the behavior of the catgut during the stretching phase before the breaking point is reached offer a means of checking the accuracy of the end point observed. It is probable that some correction factors could be worked out for the various products, based on the shrinkage and stretching phenomena observed, which would increase further the reliability of this test.

Aside from the factors of variation in the potency of the pepsin and in the rate of deterioration of the pepsin, one must consider how accurate this test is as far as any one single strand of catgut is concerned. If the test is precise, then one would expect to find that duplicate or quadruplicate tests on portions of the same strand incubated in the same solution at the same time would give end points which were practically identical. This, however, was infrequently observed, although for the most part the range of variation of the end points was within fairly reasonable bounds. In certain products a wide range of variation was sometimes observed for tests in quadruplicate on portions of the same strand of surgical gut. An extreme example of this was the results obtained on a single strand of no. 0 forty day chromic catgut. Although four portions of the same strand were subjected to digestion in the same solution at the same time, the digestion times observed were twenty-five hours, thirty-six hours, sixty-three hours and seventy-eight hours, respectively. Apparently one half of the strand was twice as resistant to digestion as the other half. One would naturally question the reliability of a test which gave such strikingly different readings on portions of the same strand of catgut. However, in checking over the data on the shrinkage and stretching phenomena it was observed that the two strands which were most rapidly digested had undergone 5 per cent shrinkage at the end of one and a half hours, as compared with 2 per cent shrinkage for the other two strands. At the end of twenty-two and a half hours there was approximately 13 per cent shrinkage in the strands which were first to break as compared with 9 to 9.5 per cent shrinkage in the others. Shortly after this reading the stretching phase

began for those two which were soon to break. The 2 more resistant strands did not reach their maximum shrinkage of 11 to 12 per cent until fifty hours, although the other 2 reached their maximum shrinkage in less than half this time. On the basis of observations such as these it is probable that the results of the digestion test expressed in hours of digestion time were reasonably accurate as far as those particular portions of the same strand were concerned. One cannot escape the conclusion that there are occasionally considerable differences in the degree of resistance of different portions of the same strand of chromic catgut. Whether these differences are due to the method of chromicizing or to the raw product is difficult to ascertain.

Some minor differences in digestion time should be expected in tests on different portions of the same strand because of the variation in the physical properties of different portions of the same strand. One may occasionally find variations of $^{3}/_{1,000}$ inch (0.05 mm.) in the diameter of any one strand at different points, and results of tests of the tensile strength may vary by several pounds. For practical purposes the range of variation of different portions of the same strand of catgut from the standpoint of its physical and absorption qualities is probably of negligible importance in most instances.

The 2 Gm. suspension pepsin digestion test offers a means of evaluating raw catgut before it has been put through any of the processes required to produce the finished surgical gut. The digestion time of the raw product undoubtedly bears some relation to the digestion time of the finished product. Furthermore, sufficient correlation might be established between the unsterilized and the heat-sterilized chromic catgut to offer a basis of evaluating the absorption qualities of the chromic catgut before it is tubed, labeled and heat sterilized. A method of determining the resistance of the chromic catgut before it has reached the stage of a finished labeled product should present obvious advantages to the manufacturer. A lot of chromic catgut which does not meet the specifications for a particular type which it is designed to be labeled can then be reclassified and properly labeled before it reaches the stage of a finished product. Trypsin digestion of catgut which has not been heat sterilized is exceedingly slow. It is doubtful whether trypsin digestion offers a satisfactory method for testing surgical gut before it reaches the stage of the heat-sterilized finished product.

In the endeavor to utilize the results and relations of the digestion tests described here for evaluating the absorption qualities of surgical gut generally, it must not be overlooked that the use of a lot of pepsin which differed appreciably in its digestive potency from that used in these tests could cause some distortion of the digestion time of the catgut tested, thereby negating the relations established with the duration of

tensile strength in the tissues. This difficulty can be overcome to some extent provided that one large source of pepsin is available for all the tests to be conducted. With this pepsin the average digestion time of a wide assortment of plain catgut from six or more companies could be taken as a base point or base unit equivalent to approximately five days' duration of tensile strength in the tissues. Twice this base unit would then be approximately equivalent to ten days in the tissues. The base unit multiplied by 3 would then indicate a suture of fifteen days' duration of tensile strength and multiplied by 4 would suggest twenty days' duration of tensile strength. By the use of a base unit such as the one described, the digestive assay of different preparations of enzymes would not substantially affect the relation of digestion time in pepsin to absorption time in the tissues. It is not unreasonable to expect that chromic catgut designed for the average surgeon should have a resistance to digestion which is at least twice that observed for plain catgut of most manufacturers. This would be approximately the equivalent of a minimum standard of ten days' duration of tensile strength for the type of chromic catgut generally used by most surgeons.

SUMMARY

A method of assaying the resistance of surgical gut (catgut) to digestion has been described as the 2 Gm. suspension pepsin digestion test. This consists of suspending a strand of catgut in a glass cylinder by a 2 Gm. weight and subjecting the catgut to the action of a solution of 0.35 to 0.37 per cent hydrochloric acid and 10 per cent pepsin incubated at 37 C. until the catgut becomes sufficiently digested to break. Also a modification of a digestion test apparatus devised by others has been described.

The digestion time in acid-pepsin solution has been determined for the surgical gut of ten different manufacturers. Most of the products have been studied over a period of three or four years. Approximately 3,200 digestion tests have been made.

By the 2 Gm. suspension test, plain catgut was found to have an average digestion time of about eleven hours, although the tests on certain products lasted twenty hours or more. Chromic catgut was found to have a rather wide range of variation, depending on the size of the catgut and the particular product. The average digestion time of chromic or tanned catgut of most companies was in excess of twenty hours, although the products of two companies were digested in a length of time which approximated the average observed for plain catgut. There were relatively minor differences in the digestion time of the twenty day and forty day chromic catgut (types C and D) of any one

company when similar sizes were compared; however, there was often a conspicuously prolonged digestion time observed for the smaller sizes of chromic catgut of some companies.

The digestion time in pepsin by the 2 Gm. suspension test was correlated with previously reported observations on the decline in tensile strength of catgut in the tissues. It was found that for the most part the digestion time in acid-pepsin solution in hours was approximately twice the number of days' duration of tensile strength in the tissues. Thus a digestion time of ten hours would indicate a surgical gut which might be expected to hold up for five days; twenty hours would indicate ten days' duration of tensile strength; thirty hours would be equivalent to fifteen days in the tissues. Although this relation was found to be moderately accurate for most surgical gut products, there were some discrepancies observed. Furthermore, the relation described would of course be materially influenced by the digestive potency of the pepsin used in duplicating these tests. A method of obviating at least to some extent the factor of variability of the digestive agent has been suggested.

CONCLUSIONS

The 2 Gm. suspension pepsin digestion test described offers a simple and rapid indirect method of evaluating the absorption qualities of surgical gut of most manufacturers within certain limitations.

Discrepancies in the reliability of digestion tests on some products will probably not be fully understood without recourse to information on details of the manufacture of surgical gut which is not generally available to individual investigators.

Any standard method of assaying catgut by digestion tests should be checked from time to time by clinical and experimental tissue implants to avoid misleading interpretations of the absorption qualities of surgical gut of the various manufacturers.

SOLITARY UNICAMERAL BONE CYST

WITH EMPHASIS ON THE ROENTGEN PICTURE, THE PATHOLOGIC APPEARANCE AND THE PATHOGENESIS

HENRY L. JAFFE, M.D.
AND
LOUIS LICHTENSTEIN, M.D.
NEW YORK

Solitary unicameral bone cyst is properly to be regarded as an independent and distinctive lesion and ought not to be included, as it still rather often is, within the omnibus and unjustifiable category of localized fibrocystic disease of bone. It is a relatively uncommon lesion and manifests itself mainly in childhood and adolescence. Nearly always it develops in the shaft of some one of a few predilected long tubular bones, and, in particular, the upper portion of the humeral shaft accounts for about one half of the localizations. Indeed, throughout this discussion, except when we are referring specifically to other localizations, we will have in mind the cyst as it appears in long bones.

Briefly and generally, the lesion can be described as a fairly large fluid-filled unicameral cavity, located in the interior of the affected bone shaft and delimited by a more or less thinned and expanded shaft cortex the inner surface of which (roughened and sometimes distinctly ridged) is lined by a rather thin membrane of connective tissue from which little material, as a rule, can be curetted away. The cyst usually attains a rather large size before its presence is discovered, and often the occurrence of pathologic fracture within its area first calls attention to its existence. The condition is readily amenable to cure by surgical intervention and occasionally even heals spontaneously after pathologic fracture. The features of solitary unicameral bone cyst which are probably the most difficult to understand are its causation and pathogenesis —questions regarding these have raised much discussion.

SOLITARY UNICAMERAL CYST IN LONG TUBULAR BONES

Age and Sex Incidence and Localization.—As noted, it is in the period between early childhood and adolescence that the great majority of patients first come under observation. Specifically, in our group of 19 cases [1] (verified, except in 1 instance, by operative and anatomic

From the Laboratory Division, the Hospital for Joint Diseases.

1. Since the time of writing, we have studied 3 additional cases. In all 3, the lesion was in the proximal part of a humeral shaft, and all 3 patients were about 9 years of age when the condition began to cause trouble.

findings), 15 patients were between 3 and 14 years of age when the condition first began to give them trouble, and the cases were rather evenly distributed over this age group. The ages of 3 of the remaining 4 patients were 16, 18 and 20 years, respectively, at the time of first observation. Thus only 1 patient was a full-fledged adult at the time when the condition first made itself felt. This patient was a man of 42 whose complaints dated back only five years. There seems to be a definite preponderance of males among the patients; in 14 of our group of 19 cases, the patients were males.

As the name solitary unicameral bone cyst indeed implies, the lesion is limited to a single focus in some one bone. As already pointed out, the most strongly predilected bone site is the proximal portion of the humeral shaft, and in 9 of the 19 cases the lesion was in that site. Next in order is the proximal portion of the femoral shaft; this was affected in 4 of the cases. It is probably safe to state that these two sites will account for about two thirds of the localizations in any representative group of cases. The precise localizations for the remaining one third are likely to show chance variation. In the group we are considering here, of the 6 cases still to be accounted for, the lower femoral shaft was involved in 2, the lower tibial shaft in 1, the upper and lower portions of the ulnar shaft in 1 each, and the upper radial shaft in 1.

Clinical Aspects.—As is generally recognized, the cyst is usually already far advanced in its evolution before its presence is discovered. Indeed, it is often not until some slight trauma, direct or indirect, has been followed by the occurrence of a pathologic fracture that medical aid is sought. Patients who do not have pathologic fracture at the time when the cyst is discovered may still give a history indicating one some time back which healed rapidly. In either case, though inquiry may reveal that the fracture had been preceded by slight recurrent local pain and some stiffness of the neighboring joint, it is remarkable, on the whole, how little difficulty there has usually been before the fracture. This often applies even in the case of involvement of a lower limb bone, but in some cases—particularly those in which the lesion is in the upper portion of a femoral shaft—attention is attracted by a limp. Altogether, when a diagnosis of the condition is made before operation, as it often is, it is usually based on the roentgen findings.

Roentgen Picture.—It is when the cyst is in the upper metaphysis of a humerus (its most common site) that the roentgen findings are most likely to guide one to the correct diagnosis. Likewise, when the cyst is in a femur, these findings not infrequently are of diagnostic aid. In relation to other long bones, the picture is not unlikely to be misinterpreted as representing some other lesion. A characteristic feature

of solitary unicameral cyst of long bones is the location in the shaft of the bone, near or relatively near to an epiphysial cartilage plate. Indeed, in a young subject the cyst rarely (if ever) transgresses the plate so as to be both in the shaft and in the neighboring epiphysis. In fact, extension to the epiphysis was not observed in any of our cases in which fusion of the epiphysis with the affected portion of the shaft had not yet taken place. Even in a case (the patient was a boy of 10) in which the cyst had come to extend through two thirds of the shaft of a humerus, the head of the bone remained unaffected. A cyst developing in a long bone after fusion of the epiphysis with the shaft may be found to involve both part of the shaft and the adjacent epiphysial end of the bone. The only instance of this kind which came under our observation was the case of a man of 42 in whom the cyst was situated in the lower end of a femur, and in this case the roentgen findings by themselves would not have led to the diagnosis of bone cyst.

This practical limitation of solitary bone cyst to the shaft at least helps to differentiate this lesion from giant cell tumor of bone, since in the latter the lesion almost invariably begins in the epiphysial end of the bone, though it may reach the shaft by extension. Further, it also seems worth noting here that the two conditions differ significantly in respect to the age distribution of the patients, solitary bone cyst occurring nearly always before the age of 20 and giant cell tumor nearly always after, as we [1a] have already pointed out in another connection.

When in the upper portion of a humeral shaft, the cyst, if seen directly or shortly after an initial infraction or fracture, is commonly found to extend from the immediate vicinity of the epiphysial cartilage plate downward for several inches (fig. 1 *A*). The diameter of the humeral shaft in the affected region may be found slightly expanded over a limited area or uniformly. The regional cortex appears attenuated. The thinning can be seen to have taken place from the medullary surface, which may even appear somewhat scalloped. The periosteal surface of the cortex is generally smooth and presents no obvious evidence of new bone apposition except in the immediate vicinity of the infraction or fracture if the latter is in process of healing. Further, on account of the disappearance of markings of the substantia spongiosa, the affected area of the shaft appears rarefied to a greater or lesser degree. In some cases, the rarefied area may appear irregularly trabeculated here and there, the so-called trabeculae actually reflecting the presence of ridges on the medullary surface of the modified cortex rather than walls traversing and dividing the cyst.

The initial cortical infraction or fracture line is usually in the proximal portion of the cystic area. The line may be transverse or oblique,

1a. Jaffe, H. L.; Lichtenstein, L., and Portis, R. B.: Giant Cell Tumor of Bone, Arch. Path. **30**:993 (Nov.) 1940.

but in any case, even if there is complete severance of continuity, this is not likely to be associated with significant displacement at the site of the fracture. The fracture tends to heal rapidly, and within a month or so continuity has usually been completely reestablished, and only a ridge in the cortex may mark the site of the previous fracture line.

Fig. 1.—Roentgenograms of a cyst occupying a substantial portion of the upper end of a humeral shaft: *A*, taken shortly after the patient had sustained the fracture shown. As can be seen, the rarefaction shadow representing the cyst is not trabeculated and extends downward from the immediate vicinity of the upper epiphysial cartilage plate. This and the other pictures pertinent to this case were placed at our disposal by Dr. H. D. Sonnenschein. *B*, taken eleven months later. Note that between the epiphysial cartilage plate and the present upper level of the cyst (the level corresponds in a general way to the site of the original fracture) a portion of the cyst has been obliterated and replaced by reconstructed metaphysis. The cyst has thus passed into its latent phase, out of the active phase shown in *A*.

Sometimes within two or three months after the first fracture one can note that the cystic area proximal to the fracture line is largely filled in with spongy bone, so that the upper limit of the cyst is now as much as an inch (2.5 cm.) below the epiphysial cartilage plate. If this process has not taken place after an initial fracture, it is common, though not inevitable, for it to follow after a second fracture has occurred, most often some months after the first and usually again through the proximal portion of the cyst.

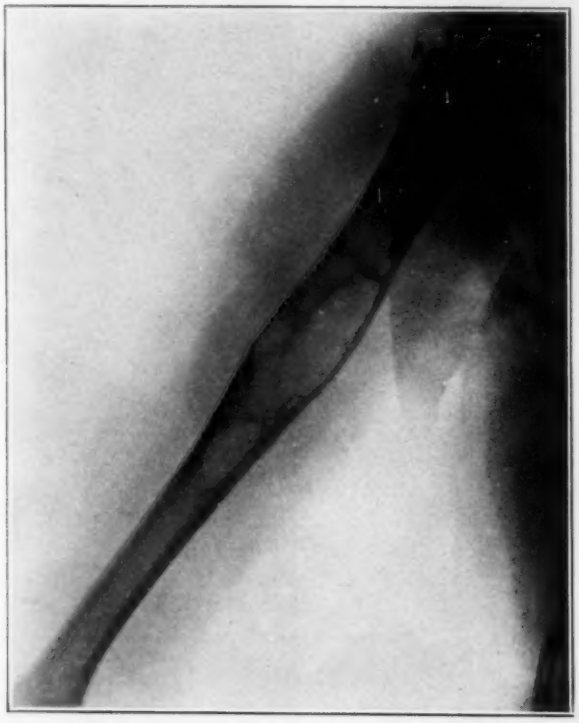

Fig. 2.—Roentgenogram of a cyst occupying the middle of a humeral shaft, the upper limit of the cyst being 3 inches (7.6 cm.) from the plate. Originally (four and a half years earlier), the upper limit had been near the plate. After a fracture then, the cyst passed from an active into a latent phase and gradually moved down the shaft. At the time of writing, it has been in a latent phase for at least four years (as intervening roentgenograms show). However, it did not undergo spontaneous healing or obliteration, even though there had been a second fracture through it ten months before this roentgenogram had been taken, i. e., when the cyst had already been in its latent stage for a long time.

Thus, within a year after the first or even less time after the second fracture, an inch (2.5 cm.) or more of reconstructed metaphysis may be present between the plate and the upper end of the cyst (fig. 1 *B*). At the same time, the longitudinal axis of the cyst may be found

reduced but is not necessarily so, since the cyst may have progressed somewhat at its distal end. In time, in consequence of growth of the bone and reconstruction of the metaphysis between the upper end of the cyst and the plate, the cyst may move a considerable distance down the shaft. Indeed, in 1 of the cases, four and a half years after the initial fracture, the proximal end of the cyst was 3 inches (7.6 cm.) from the plate (fig. 2).

Should there be no such filling in of the metaphysis after a succession of fractures, the cyst usually shows additional progression and may come to occupy a substantial portion of the shaft. In one of the cases—that of a boy of 16 who had had a series of fractures (the first occurring at the age of 11)—the cyst occupied almost all of the upper half of the humeral shaft. In another case—that of a boy of 10—the cyst came to occupy the upper two thirds of the humeral shaft. In this case, the growth of the bone was retarded, the affected humerus being several inches shorter than the one on the opposite side, apparently because during a long part of the period of active growth of the bone, the cyst did not move away from the plate (fig. 3).

A cyst in the upper end of a femur, observed directly or shortly after an initial fracture, is likely to be found extending from the vicinity of the plate belonging to the head into the neck and onward somewhat beyond the trochanters and thus also to have a long axis of several inches. In a case in which a few months have elapsed between the fracture and the roentgen examination, one may find that much of the neck has been reconstructed, and the cyst may even be situated between and below the trochanters. On the other hand, if, on account of pain and limp, the patient came under observation before fracture has occurred, the upper end of the cyst may even still be abutting on the plate. In the lower femoral shaft of a patient who is still a youth and presents a history of fracture some months before, it is likely to be found that the cyst has moved upward from the plate. Altogether, cysts of the femur (whether in the upper or the lower portion of the shaft) tend to present essentially the same roentgen picture as those in the upper part of the humeral shaft, though the picture is not so characteristic as when the lesion is in the latter site.[1b]

1b. Not directly pertinent to the lesion under discussion, but of interest in connection with the general question of cystlike rarefactions in bone are the cystlike areas observed by Sontag and Pyle (Sontag, L. W., and Pyle, S. I.: The Appearance and Nature of Cyst-Like Areas in Distal Femoral Metaphyses of Children, Am. J. Roentgenol. **46**:185, 1941) rather frequently in girls and more frequently in boys in the course of serial skeletal examinations of normal children. Specifically, they found small cystlike rarefactions, somewhere between 0.5 and 1.5 cm. in diameter, on the medial aspect of one or both lower femoral metaphyses in the cases in question. The rarefactions were completely asymptomatic, were usually already present by about 4 years of age and usually disappeared spontaneously within the following two years.

In other long bones, the cyst, when first observed, is not uncommonly found to have moved several inches away from the neighboring plate. Thus a boy of 16 having a cyst in the upper part of a radial shaft showed the cyst beginning 2½ inches (6.35 cm.) below the plate

Fig. 3.—Roentgenogram of a cyst which, because it remained in an active phase, came to occupy fully two thirds of a humeral shaft. The affected portion of the shaft was found to be represented merely by a thin, and in places even parchment-like, somewhat ridged cortical shell enclosing a fluid-filled cavity from the wall of which only a few curet spoons of material could be obtained. This picture and the other one pertinent to this case were placed at our disposal by Dr. Henry Milch.

of the head and extending 3 inches (7.6 cm.) down the shaft. In a girl of 14 whose cyst was in the lower part of an ulnar shaft, it began 1½ inches (3.8 cm.) from the plate and extended 1½ inches up the shaft. In a girl of 10 whose cyst was in the lower part of a tibial shaft, it began 2 inches (5 cm.) from the plate and extended 2½ inches (6.35 cm.) up the shaft. On the other hand, in a boy of 8 having pain and disability at the elbow of only two weeks' duration, the cyst was smallish, extending from just below the coronoid process of the ulna downward for only an inch (2.5 cm.). In 2 of these 4 cases in which the cyst was in some long bone other than a humerus or a femur, the cyst did not even extend across the entire width of the affected part of the bone. Further, in none of the cases could one be reasonably certain on the basis of the roentgen picture alone that one was dealing with a cyst (fig. 4 *A* and *B*). In particular, the roentgen picture presented by these lesions of long bones could not readily be distinguished from that seen in certain cases of solitary fibroma (osteogenic or nonosteogenic) or enchondroma or in connection with a localized focus of fibrous dysplasia.[2]

Pathologic Appearance.—In the course of exposing the cyst, the surgeon finds the overlying muscles unaltered, unless there has been a recent fracture, in which case they are likely to be discolored from hemorrhage. When the muscles are retracted, the cortical wall of the cyst may present a bluish sheen, apparent even through the periosteum, accounted for by the thinness of the cortex and its consequent translucency to the fluid in the cyst. Indeed, in some places the cyst wall may be of almost eggshell thinness. When the periosteum is stripped off, it may be found that where the cortex is especially attenuated, parts of the latter may even show tiny defects. The fluid which is evacuated when the cortex is cut through may be clear and yellowish or else serosanguineous. If there has been a recent fracture through the cyst, the fluid is likely to be heavily discolored by blood, and the cyst may even contain coagula of blood. In only 1 of our cases (that of a smallish lesion in the upper metaphysis of the ulna) did it appear from the surgeon's note that there was no fluid in the cyst.

On evacuation of the fluid and exploration of the cavity, the latter is found not to be divided off into compartments. However, the inner wall of the cortex may show some meager bony ridging, and in an occasional case a few projections may be found jutting prominently into the cavity. Further study commonly shows that the inner surface of the cortex is lined by a connective tissue membrane which, most often, is smooth and thin. If the fluid content was not frankly sanguineous, the basic color of the membrane will be gray white, though

2. Lichtenstein, L.: Polyostotic Fibrous Dysplasia, Arch. Surg. **36**:874 (May) 1938.

patches of it may show rust brown discoloration. If one curets the inner wall of a cyst, it is striking to find how little tissue can usually be obtained. A cyst several inches in length may yield only 2 or 3 curet spoons of material. Occasionally, however (as was shown in 2 of our lesions, each in the lower end of a femur), a considerable amount of yellowish and brownish material, obviously containing a good deal of lipoid, could be curetted from a few places on the cyst wall.

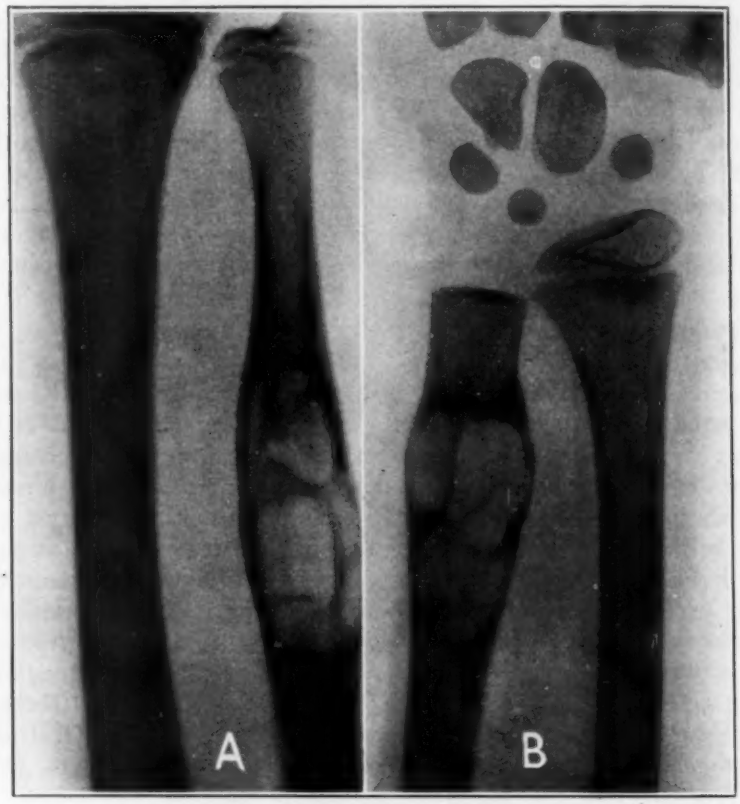

Fig. 4.—*A*, roentgenogram of a solitary unicameral cyst in the shaft of an ulna. The cyst is in a latent phase, and its distal end is about 1½ inches (3.8 cm.) from the distal plate. For this picture we are indebted to Dr. Samuel Kleinberg. *B*, roentgenogram of a nonosteogenic fibroma of an ulnar shaft. In this case, the area in question was found completely filled with firm brownish fibrous tissue consisting histologically of whorled bundles of spindle connective tissue cells moderately interspersed with smallish, often elongated, multinuclear giant cells. From the roentgenogram alone, one could not have been at all certain that one was not dealing with a cyst in this case too. For this picture we are indebted to Dr. Isaac Reitzfeld.

On microscopic examination, the thin cortical wall of the cyst is found composed of rather loose-meshed osseous tissue (fig. 5). This represents a new cortex which has slowly been laid down by the periosteum as the old cortex was being resorbed. It is only at sites of infraction that obvious signs of active periosteal new bone apposition are present. The fairly large vascular spaces of the cortical shell usually show many dilated and thin-walled vessels. On the walls of these spaces, a scattering of osteoclasts may be seen, and some osteoclasts

Fig. 5.—Photomicrograph (× 30) showing the histologic details at one point in the cortical shell of the cyst pictured in figure 3. In the area in question, the cortex was not nearly as thin as it was, on the whole, elsewhere. The lining of the inner surface of the cortex (upper margin in the picture) is a mere membrane of connective tissue. Below it can be seen the osseous tissue, permeated by large spaces containing vessels. At the lower margin of the picture, the outer surface of the cortex can be seen, devoid of periosteum, which had been stripped away at the operation.

may be present also between the periosteum and the outer surface of the cortical shell on the one hand and between its inner surface and lining membrane on the other.

As noted, this membrane is thin in most places, consisting in these of only a few superposed layers of connective tissue cells. In other places, the membrane may be slightly thicker and be composed essentially of rather vascular connective tissue. It may also show a scattering of blood pigment, either free or within phagocytes. Here and there in the lining membrane, some osteoid and osseous trabeculae may be seen to have formed through metaplasia. The bits of tissue which are usually found adherent to the lining of the cyst will appear on microscopic

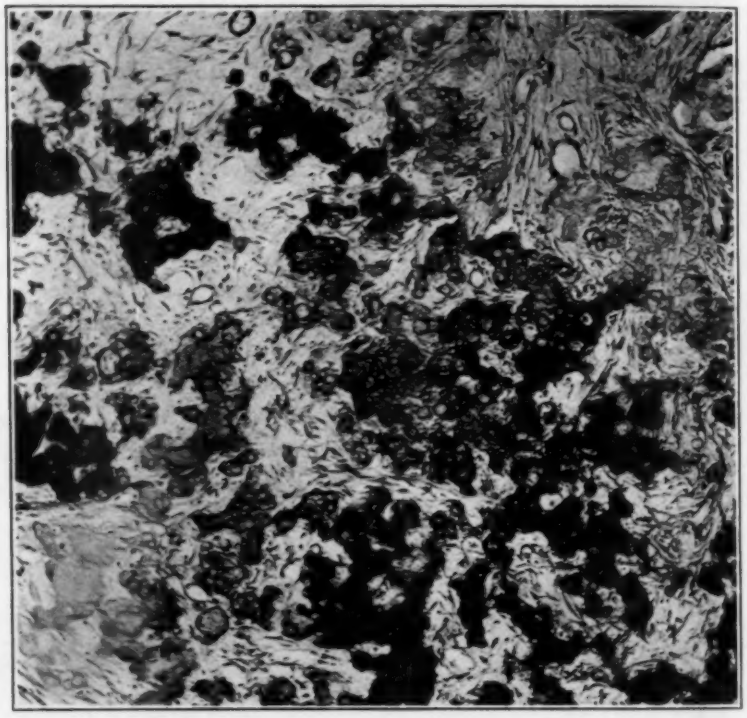

Fig. 6.—Photomicrograph (× 115) showing the histology of the bits of organizing and calcifying fibrin and blood clot which are not infrequently curetted from the wall of a cyst. The agglutinated masses of fibrin and red blood cells are enmeshed in a moderately vascularized substratum of delicate connective tissue cells. The darkest areas represent those in which the calcification is most intense.

examination to be mainly fibrin clots, often containing some red blood cells and undergoing organization and even calcification and ossification (fig. 6). In 1 of the 2 cases mentioned in which a relatively generous amount of brownish material could be curetted from some places on the cyst wall, this material consisted mainly of cholesterol crystals embedded

in fibrin (fig. 7). In the other, the material included crystals, but also foam cells, hemosiderin-bearing phagocytes and many foreign body giant cells. Any substantia spongiosa that may have been removed from beyond the immediate limits of the cyst is likely to show remodeled trabeculae, while the intertrabecular marrow appears mucoid or fibrous and contains thin and dilated blood vessels.

Causation and Pathogenesis.—At least before the hyperparathyroid basis of Recklinghausen's disease had been demonstrated, some were

Fig. 7.—Photomicrograph (× 115) showing the histology of the brownish material which is occasionally found adherent to the wall of a cyst. Note the spaces representing the shape of cholesterol crystals previously present and the foreign body giant cells about these spaces. Some hemosiderin-containing phagocytes and some lipophages also are present.

willing to assign the same origin to solitary unicameral bone cyst as to the bone cysts in the former disease. Thus, building on the conception held by Engel [3] of the bone cysts in Recklinghausen's bone disease,

3. Engel, G.: Ein Fall von cystoider Entartung des gesammten Skelets, Thesis, Giessen, F. C. Pietsch, 1864.

some authors have interpreted solitary bone cyst as resulting from hemorrhage after vessel tears in an area of bone softening. While not entirely implausible, this theory leaves the hypothetic bone softening undefined and unexplained, and it has been generally discarded. Others, including Recklinghausen [4] himself and Schmidt,[5] have conceived of solitary bone cyst as representing simply an area of fibrous osteitis which has undergone cystic degeneration. This theory is rendered highly implausible by the facts that curettement of the wall of a solitary unicameral cyst rarely yields, as has been noted, more than a few tiny fragments of tissue at all, and that on microscopic examination such tissue as can be obtained proves to be mainly fibrin or blood clot in various stages of alteration and not the kind of tissue which one obtains from a cystically softened solitary fibroma or focus of fibrous dysplasia in bone. Running parallel with this fibrous osteitis theory there was the conception, proposed by Virchow,[6] that solitary bone cyst represents a central bone tumor and in particular some sort of chondromatous lesion which has likewise undergone cystic softening; here again is a conception which lacks basis in fact.

According to another theory, which is still in good favor in some quarters, solitary bone cyst represents a healing form of localized osteitis fibrosa or tumor-forming localized osteitis fibrosa—that is, of so-called giant cell tumor. This idea seems to have been fathered by Mönckeberg,[7] developed by Konjetzny [8] and adopted also by Geschickter and Copeland.[9] It is true that a giant cell tumor may undergo partial cystic degeneration. However, it is difficult to understand why this fact should necessarily lead to the interpretation of solitary bone cyst as a healing form of giant cell tumor. In the first place, as already pointed out, giant cell tumor appears at a definitely later age, on the average, than solitary bone cyst. Further, a giant cell tumor nearly always starts in an epiphysis, while a solitary bone cyst nearly always starts in a metaphysis and only rarely transgresses into the epiphysis. In addi-

4. von Recklinghausen, F.: Die fibröse oder deformierende Ostitis, die Osteomalacie, und die osteoplastische Carzinose in ihren gegenseitigen Beziehungen, in Festschrift Rudolf Virchow zu seinem 71. Geburtstag gewidmet, Berlin, G. Reimer, 1891.

5. Schmidt, M. B.: Allgemeine Pathologie und pathologische Anatomie der Knochen, Ergebn. d. allg. Path. u. path. Anat. **7**:221, 1900-1901.

6. Virchow, R.: Ueber die Bildung von Knochenzysten, Sitzungsb. d. Akad. d. Wissensch., Berlin, 1876, p. 369.

7. Mönckeberg: Ueber Cystenbildung bei Ostitis fibrosa, Verhandl. d. deutsch. path. Gesellsch. **7**:232, 1904.

8. Konjetzny, G. E.: Die sogenannte "lokalisierte Ostitis fibrosa," Arch. f. klin. Chir. **121**:567, 1922.

9. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, revised ed., New York, American Journal of Cancer, 1936, p. 243.

tion, again as already stated, a solitary cyst usually has few if any tissue masses adherent to its wall, and when they are present their histologic architecture does not correspond to that of a genuine giant cell tumor. The bits of tissue may indeed show, among other elements, a sprinkling of giant cells, especially in relation to areas of hemorrhage, but these cells are not embedded in a stromal tissue of the kind seen in giant cell tumor.[1a]

A much more cordial reception has been given to the theory advocated by Pommer.[10] According to this theory (based on histologic study of 1 case), solitary bone cyst results from the encapsulation and alteration of a focus of intramedullary hemorrhage. It is thought that after the affected area has been encapsulated, it is kept distended by transudation of fluid into it and that pressure from the cyst causes stagnation in the blood and lymph channels about it, pressure erosion of the neighboring bone and finally even expansion of the overlying cortex. This theory is confronted with the obvious objection that cysts do not follow on fractures, though the latter are, of course, associated with hemorrhage. To meet this objection, the proponents of the Pommer theory (e. g., Lang [11]) argued that when fracture occurs, the periosteum is torn, and the possibility of developing a closed pressure cyst is removed. Hence it is postulated that it is only after mild trauma without fracture but with intramedullary hemorrhage that bone cysts on a hemorrhagic basis develop.

Mikulicz [12] at least recognized that solitary bone cyst (which he designated osteodystrophia cystica juvenilis) constitutes a disease entity. Further, he held that its predilection for young subjects and for regions of active growth of long bones suggest that it represents some local disturbance in bone growth and development. In fact, he held that it represents a local post-traumatic dystrophy. Mikulicz' conception of the causation of solitary bone cyst has not received general recognition. However, it seems to us that (except for its inclusion of the dubious idea of a traumatic factor as the instigator of the growth disturbance), this conception has much in its favor.

One evolutionary feature of the lesion in question which seems not to have been sufficiently emphasized and which has attracted our attention is that the cyst may pass from an active into a latent phase. Specifically, a cyst which extends to the immediate vicinity of, or abuts

10. Pommer, G.: Zur Kenntnis der progressiven Hämatom- und Phlegmasieveränderungen der Röhrenknochen, Arch. f. orthop. u. Unfall-Chir. **17**:17, 1920.

11. Lang, F. J.: Beiträge zu den mikroskopischen Befunden bei Knochenzysten, Deutsche Ztschr. f. Chir. **172**:193, 1922.

12. von Mikulicz, J.: Ueber cystische Degeneration der Knochen, Verhandl. d. Gesellsch. deutsch. Naturforsch. u. Aerzte **76**:107, 1906.

on, an epiphysial cartilage plate must be regarded as an active one still possessing potentialities for growth. On the other hand, a cyst which has definitely moved away from the plate, so that there is now a reconstructed area of shaft between it and the plate, has entered into the latent stage of its life cycle, for its growth activity has ceased. The lesion may now be regarded as merely a static defect in the bone, though this defect may maintain itself for years and even be the basis for subsequent refrac-

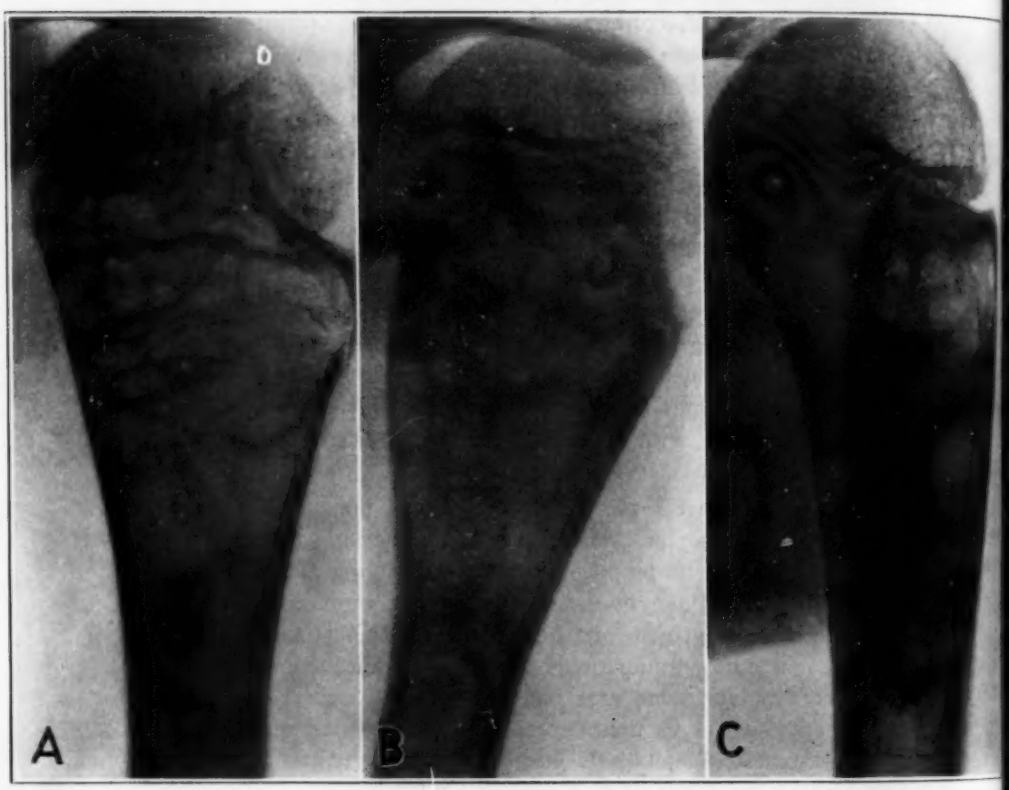

Fig. 8.—*A*, roentgenogram showing a somewhat trabeculated rarefaction shadow representing a cyst in the upper end of the humeral shaft with an infraction in the cortex. This picture was taken ten days after the patient had had a sudden attack of pain while swimming. *B*, roentgenogram showing the appearance of the affected area two months later. Note how opaque this area appears in comparison with what it was. *C*, roentgenogram showing recystification of the area, fourteen months after the picture shown in *A* had been taken. Except for support of the area while the fracture was healing, no treatment other than some baking and massage was given. In a roentgenogram taken six months after the one illustrated in *C*, the appearance was essentially the same.

tures. It is in this latent and static stage that the cysts heal most promptly in response to curettage and filling with autogenous bone chips.

Treatment.—Apparently a solitary bone cyst occasionally becomes spontaneously filled in (after a fracture) as is demonstrated by the course in the case described by Adams.[13] However, this course is much more exceptional than it has often been thought to be. A cyst of the upper part of the humeral shaft from a case in our series showed what appeared to be spontaneous rapid filling in after an infraction of the cortex from slight trauma. However, fourteen months later, though the cortex of the affected area was now fairly thick, the substantia spongiosa again appeared cystic. Indeed it was now multicystic, as though partitioned off into a number of small cavities. What had apparently occurred was that the lesion had changed from a unicameral cyst with a thin cortex to a multicameral cyst the cortex of which was thick in some places so that although the cyst had not healed in completely, no further clinical difficulty was to be anticipated (fig. 8).

In describing the roentgen picture of bone cyst, it was pointed out that some months after the initial fracture, but more often after the second or third fracture, it will be observed that an area of reconstructed metaphysis is present between the cyst and its neighboring epiphysial cartilage plate. In the discussion of the pathogenesis, it was emphasized that if the cyst has moved away from the neighboring plate, the growth activity of the cyst has ceased, the latter having changed from active to static (figs. 1 *B* and 2), and that static cysts are highly amenable to surgical intervention.

The treatment of choice (whether or not the lesion has moved away from the plate) is to expose the cyst, curet its wall, fill it with autogenous bone chips (e. g., from the tibia), collapse the cyst wall and close the wound tightly. This procedure can be expected to yield a cure in most cases, and indeed it did so promptly in all of our cases in which the cyst was static at the time of surgical intervention (fig. 9 *A*). On the other hand, in 2 cases in which the cyst was still abutting on the plate at the time of operation (1 of the cysts was also heavily radiated before operation), prompt healing did not take place after curettage and introduction of bone chips. In both cases, large cystic areas reappeared, and in both cases pathologic fractures recurred. However, also, in both instances, even without a second surgical intervention, a good deal of healing was subsequently observed (fig. 9 *B*). The course of this could have been expedited by a second intervention, with renewed curettage and refilling with bone chips.

In no case did we find that any benefit resulted from radiation therapy. Certainly this therapy does not favor healing of the cyst

13. Adams, A. W.: Report of a Case of Solitary Fibrocystic Disease of the Humerus Exhibiting Spontaneous Resolution, Brit. J. Surg. **13**:734, 1926.

without surgical intervention. On the other hand, when given before or after such intervention, there is at least the theoretic possibility that it may even delay healing.

Fig. 9.—*A*, roentgenogram showing, in a healed condition, the cyst pictured in figure 1 *A* and 1 *B*. This picture was taken only four months after bone chips had been introduced into the cyst, which, as 1 *B* shows, was already in a latent stage. *B*, roentgenogram showing the status of the humeral cyst pictured in figure 3, but four and a fourth years after it had been filled with autogenic chips and slivers of bone. Comparison between the figures reveals the thorough reconstruction which has taken place in the proximal portion of the affected shaft and shows, altogether, that much of the deformity has corrected itself. It is true that the middle of the shaft is still cystic and shows a recent transverse fracture. However, the cyst is now in a latent stage, and there is every indication that rapid and complete healing will take place, especially if the area is again filled with bone chips.

SOLITARY UNICAMERAL CYST IN BONES OTHER THAN LONG TUBULAR BONES

Our own hospital records from 1925 to date include no case in which a solitary unicameral cyst of a kind entirely analogous to that appearing in long tubular bones was found in some other bone. It is perhaps worth noting, however, that we did encounter, as an incidental finding in a rib, a cyst which, while multicameral at the time of removal, looked as though it might have been a unicameral cyst which had undergone only partial spontaneous healing. Altogether, our experience is not out of harmony with the acknowledged rarity of solitary unicameral bone cyst in other than long tubular bones. Of the supposed instances reported, it is possible that some of those in which the lesion was in a metacarpal or a metatarsal bone shaft actually do represent such cases, since the development and structure of these short tubular bones is parallel to that of the long tubular bones. However, reservations are in place even in regard to these supposed instances. For example, among the cases described by Platt [14] as instances of cyst of the tubular bones of the hand or the foot there are only 1 or 2 that may possibly be such, and even these must be accepted with reservation. The occurrence of this cyst in bones which develop like epiphyses from a single center of ossification (e. g., the astragalus) seems rather unlikely, since the cyst appears to start its development not in epiphyses but instead in a shaft region abutting on an epiphysial cartilage plate.

ANEURYSMAL CYST

Under this heading, we wish to call attention to a peculiar blood-containing cyst of large size which, though its precise nature is not yet clear, seems to match more closely with unicameral bone cyst than with any other type of cyst. Possibly some of the cases described as instances of aneurysmal giant cell tumor and benign bone aneurysm actually represent this lesion, of which we have studied 2 examples.

In 1 case—that of a boy of 17—the cyst involved the superior ramus of the pubis and caused such pronounced distention of this bone, especially inward and backward, that an expansion of the pelvic wall as big as a large orange could be felt through the rectum. In the roentgenograms the affected bone area presented a coarse soap bubble appearance (fig. 10). In the second case—that of a boy of 18—the cyst involved the second dorsal vertebra, having cystically transformed and expanded the body, the arch and the spinous process. The expanded body was luxated anteriorly, and, in addition, the cyst had caused pressure erosion of several neighboring ribs on the left side and of a part of the third

14. Platt, H.: Cysts of the Long Bones of the Hand and Foot, Brit. J. Surg. **18**:20, 1930.

vertebra. In the roentgenogram, one could see that in this case, too, the altered body had a somewhat coarse soap bubble appearance. As was to be expected in view of the location and the size of this lesion, the patient already showed a number of abnormal neurologic manifestations on admission to the hospital; specifically, transverse myelitis developed after the cyst was explored.

In both cases, when exposing the lesion and opening into its thin wall, the surgeon was immediately confronted by a large hole containing much fluid blood, and the exudation of blood continued, though without spurting; the supply apparently came steadily from the inner wall of the

Fig. 10.—Roentgenogram of an aneurysmal cyst which has completely replaced a superior pubic ramus.

cyst. On microscopic examination, the wall's lining tissue, which in many places was not thick, was found elaborately vascular (fig. 11). Specifically, the connective tissue composing the lining wall was heavily permeated with delicate blood-filled capillaries and large distended or distorted venous channels. In some places, there was much free hemorrhage between the blood channels, and in these areas hemosiderin-bearing phagocytes and multinuclear giant cells were sometimes numerous. In fact, some of the larger venous spaces were even collared by collections of multinuclear giant cells. Further, between the vascular spaces and sometimes even around the larger ones, there were filamentous trabeculae

of connective tissue bone. The numerous and intercommunicating vascular channels were the source of bleeding into the cyst proper, and, indeed, when the cavity was entered, blood continued to flow copiously from it. However, in these cases, the absence of blood clot on the wall indicated that the blood in the cavity was not stagnant, and the blood-filled cavity could be regarded as being merely a large venous pool being steadily drained and freshly supplied.

The treatment of choice for such aneurysmal cysts is essentially like that for solitary unicameral bone cyst, namely, curettage of the wall and

Fig. 11.—Photomicrograph (× 20) of part of the wall of the cyst shown in figure 10. Note the abundant vascular spaces, some of which are large and supported by filamentous trabeculae of connective tissue bone.

packing of the cavity with autogenic bone chips. The baneful consequences of intervention in the case in which the lesion was present in the dorsal vertebra were due solely to the peculiarly unfortunate location of the cyst.

SUMMARY

Solitary unicameral bone cyst is a lesion sui generis. It bears no relation whatever to giant cell tumor of bone, and in particular it does not represent a cystic-healing phase of this tumor. Nor is it to be linked

with enchondroma, fibroma or focus of fibrous dysplasia of bone which has undergone partial or extensive cystic degeneration. Further, it should not be regarded as representing the cystic expression of osteitis fibrosa, since to throw it into this wastebasket category (one which to us is also meaningless) is to obliterate its distinctiveness. Correspondingly, solitary unicameral bone cyst ought no longer to be classed as an expression of localized fibrocystic disease of bone or localized fibrous osteodystrophy—likewise blanket designations dating from a more primitive era of bone pathology.

Practically always, the lesion begins its development in the shaft, at or near an epiphysial cartilage plate, of some one of a few predilected long tubular bones. Indeed, in any representative series of cases, about half of the lesions will be found in the upper humeral shaft, and this region, together with the upper femoral shaft, will account for fully two thirds of all cases. The cyst is usually already large and well developed when attention is first drawn to its presence—usually by an infraction of the attenuated cortex. Anatomically, the lesion presents itself as a unicameral cavity filled with fluid and delimited by a thinned and often distended shaft cortex. The inner surface of this cortex, roughened and sometimes distinctly ridged, is lined by a rather thin connective tissue membrane yielding, as a rule, but little material to curettement. On microscopic examination, this material is found to consist mainly of fibrin clots containing some red blood cells and undergoing organization and even calcification and ossification. In an occasional case it also contains some cholesterol crystals, with or without nests of multinuclear giant cells and lipoid and hemosiderin-containing phagocytes.

As to pathogenesis, we favor the view, already proposed by Mikulicz,[12] that the lesion has its basis in a local disorder of development and bone growth, rather than, as proposed by Pommer,[10] in a local intramedullary hemorrhage resulting in the development of an encapsulated pressure cyst from the continuous transudation of fluid into the area. We have tried to show also that the natural life cycle of the cyst has two stages. The first stage—that of active growth—persists as long as the cyst remains abutting on the epiphysial cartilage plate. The stage is usually interrupted when an area of substantia spongiosa becomes reconstructed between the plate and the cyst, in the course of healing of a spontaneous fracture. The cyst is then in the second stage—the latent or static—in which, while tending not to increase in size, it moves farther away from the plate as the longitudinal growth of the bone progresses.

Whether in the growing or in the static stage, solitary unicameral bone cysts are amenable to operative cure by curettage and filling with autogenous bone chips. Indeed, if the cyst is in a latent stage, it is almost

sure to show prompt obliteration in response to this treatment. If the cyst is still in its growing stage, it is often likewise quckly obliterated. However, particularly large cysts in this stage, or cysts which have been irradiated before being operated on, may fail to fill in completely and promptly, sometimes requiring a second intervention. Finally, it appears that spontaneous (nonsurgical) healing of solitary unicameral bone cyst occurs much less frequently than is commonly supposed. Radiation therapy by itself never leads to healing of the type of cyst in question and seems even to be contraindicated as an adjuvant to surgical intervention.

Attention has also been drawn to the rarity of solitary unicameral cyst in other than long tubular bones and to a peculiar type of blood-containing cyst which was described under the heading of aneurysmal cyst.

RECURRENT DISLOCATION OF THE PATELLA

A STUDY OF END RESULTS IN TWENTY-SEVEN CASES

S. SVERRE HOUKOM, M.D.
Formerly Anne C. Kane Fellow, New York Orthopaedic Dispensary and Hospital
DULUTH, MINN.

The treatment of recurrent dislocation of the patella has been a fertile field for the growth and development of surgical ingenuity. As many as sixty different operative procedures have been devised for its correction. This study of 27 dislocating patellas treated at the New York Orthopaedic Dispensary and Hospital confirms my belief that one or two types of procedure, either separate or combined, are sufficient to give a stable symptomless knee. This is true for all types of cases. It is important also to emphasize relatively early operative treatment, since with this condition osteoarthritis is prone to occur sooner than in a normal knee.

CLINICAL FINDINGS

The group of cases here presented comprises 10 in which the condition was bilateral and 7 in which it was unilateral, or a total of 27 dislocating patellas which were treated by operation at the New York Orthopaedic Dispensary and Hospital in a thirteen year period between 1925 and 1938.

History.—Sex: All of the patients were female. This predominance among the female sex was found also among 27 patients seen in the dispensary but not admitted to the hospital for treatment. Only 3 of these clinical patients were male.

Age of Onset: The chronic recurrent type of dislocation has its onset chiefly in late childhood or early adolescence. The age of onset varied from 3½ to 16 years, the average age of onset in 14 cases being 9.9 years.

Trauma: None of the patients gave a history of violent or severe trauma. Six gave no history of trauma at all. In 7 patients, the initial dislocation occurred when the patient was engaged in fairly strenuous activity, such as running, jumping or bending over. The recurrent attacks usually occurred also when running, jumping or doing acrobatic dancing. In 1 patient, the patella dislocated on ordinary walking. In 2 patients, the patella slipped when the knee was flexed. Three patients

From the New York Orthopaedic Dispensary and Hospital.

reported that their knees merely gave way and they fell and that because of this, they were unable to play games.

Joint Reaction: A severe joint reaction did not usually occur after this type of dislocation. A few patients did not have any pain. Most patients had moderate pain and swelling lasting a few days. Several patients had only momentary pain which disappeared as soon as the knee was moved and manipulated and the patella slipped back into place.

Frequency of Attacks: The frequency of dislocation varied greatly, occurring only once or twice a year in some patients; in others, as often as a dozen times a month. Although severe joint reactions are uncommon, the frequency of attacks in some cases must certainly cause chronic irritation in the joint, leading to osteoarthritis.

Physical Examination.—General Findings: On physical examination, most of these patients did not show any noteworthy findings besides the local knee condition. One patient had mild residual poliomyelitis, but the muscles of the involved knee were not appreciably affected, all muscle weakness being below the knee. Another patient had considerable shortening on the affected side (3½ inches [8.9 cm.]) due to growth disturbances in the epiphysial plates of the femur resulting from fracture in infancy. General ligamentous relaxation was noted in 4 cases.

Valgus Deformity of the Knee: Nineteen knees had valgus deformity varying from slight to 20 degrees. In 10 of these, the valgus was not more than 5 degrees. In the remaining 9 cases, the valgus varied from 5 to 20 degrees. One third of the entire group of 27 cases, therefore, had an appreciable degree of knock knee, which may have been a predisposing cause of dislocation.

Patellas: Three patellas were reported as being underdeveloped. Three had tight fascial bands on the lateral side. In 13 knees, the patella was said to be abnormally movable. It is difficult to say at what point a patella has abnormal mobility. With the knee in full extension, the normal patella has a considerable free range of motion both medially and laterally when the quadriceps muscle is relaxed. I have seen patients preoperatively in whom the amount of passive mobility of the dislocating patella did not seem greater than on the unaffected side.

Lateral Femoral Condyle: In only 1 case was the lateral femoral condyle stated to be underdeveloped in the preoperative examination. The only way that aplasia of this structure can be definitely determined is by exposure of the lateral condyle at the time of operation.

Quadriceps Muscle: Abnormalities of the quadriceps muscle were infrequent. In 1 case there were considerable atrophy and poor power. In 1 case in which the condition was bilateral, active extension of the knees was limited to 160 degrees, presumably owing to poor quadriceps power.

Knee Motion: All knees had full passive motion except in 1 case in which there was bilateral knee flexion deformity of 5 degrees. In 1 case in which the condition was bilateral there was marked ligamentous relaxation of the knee, and in 3 others, slight relaxation.

Gait: The gait was not abnormal unless an associated deformity, such as a short leg, was present.

Roentgen Findings.—In the roentgen examination of these patients, the usual anteroposterior and lateral views of the knee were taken. In addition, an anteroposterior view with the knee in acute flexion also was taken. This gives a good view of the patella resting in the intercondylar groove and its relation to the condyles of the femur.

The roentgenograms reproduced in this article show that marked structural abnormalities are uncommon. Some of the features which should be noted are:

1. Genu valgum of varying degree, which is easily seen, may be present.

2. The patella may be higher and more laterally placed than normal (fig. 1 *A*).

3. Lateral roentgenograms may show that the patella has slipped off with the knee in extension. This is the more common occurrence (fig. 2 *A*).

4. Occasionally, lateral roentgenograms show that the patella has slipped off with the knee in flexion (fig. 3 *B* and *C*, right knee).

5. In cases of the congenital type, the patella is dislocated laterally both in flexion and in extension (fig. 4 *A* and *B*).

6. The lateral condyle may be underdeveloped. Aplasia of this structure is difficult to determine by roentgen examination. Figure 4 *A*, which shows the anteroposterior view of the knee in flexion in a case of the congenital type, might be interpreted as showing underdevelopment of the lateral condyle. However, this view shows the more distal portion of the condyle, and at this level the lateral condyle has normally less elevation than the medial condyle.

Classification of Dislocating Patellas.—Cole and Williamson [1] divided their cases of dislocation of the patella into three different groups as follows: (1) acute traumatic dislocation, which may be an occasional cause of chronic recurrent dislocation; (2) congenital dislocation, in which the patella has developed away from its normal position and has never been where it belongs—the patella is found on the lateral side, resting firmly against the lateral femoral condyle; (3) chronic recurrent dislocation, usually due to certain underlying predisposing causes, the

1. Cole, W. H., and Williamson, G. A.: Chronic Recurrent Dislocation of the Patella, J. A. M. A. **102**:357-360 (Feb. 3) 1934.

majority of which occur without any acute trauma. In addition to these types, 2 of the cases in the group on which this study is based are classified under a separate heading because of severe knock knee deformity due to growth disturbances. One other case is classified separately because of poliomyelitis involving the extremity.

Using these criteria, the 27 dislocating patellas in this group were classified as follows: adolescent, 20; congenital, 4; due to severe knock

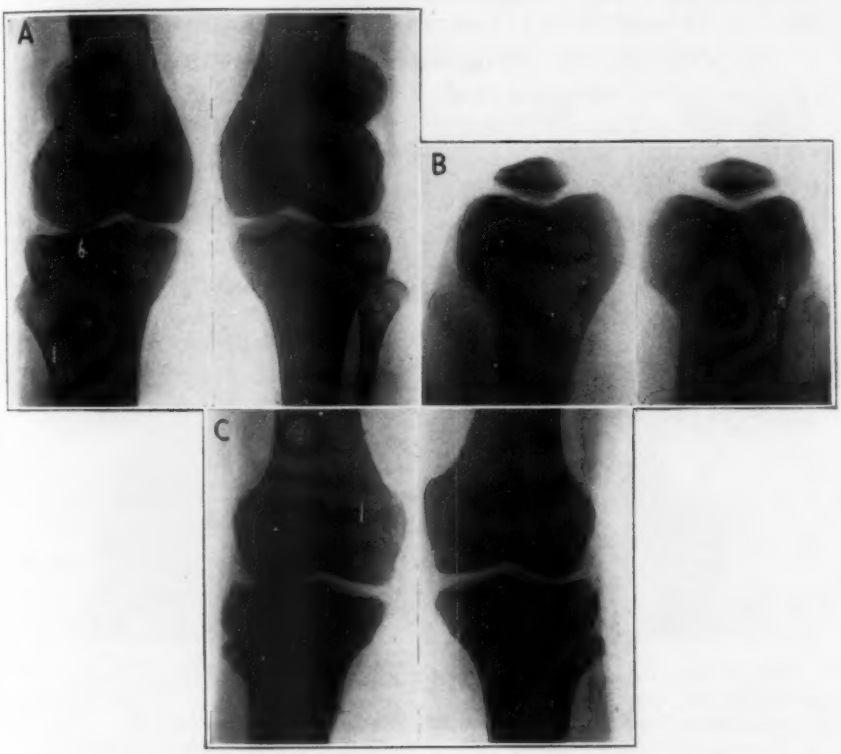

Fig. 1.—Roentgenograms of a patient with bilateral dislocating patella. In this case the patellas dislocated with the knees in extension. *A*, anteroposterior view before operation with the knees in full extension. The patellas are riding higher on the femur than usual. *B*, anteroposterior view before operation of the knees in acute flexion. In this position the patellas are in normal relation to the femoral condyles. *C*, after bilateral tibial tubercle transplant operation. The patellas are now resting in the proximal portion of the trochlear fossa in a more medial and distal position than before operation.

knee caused by (*a*) fracture in infancy and (*b*) chondrodysplasia, 2; due to residual poliomyelitis, 1; traumatic, 0.

The physical and roentgen examinations of these patients showed no marked deviation from normal in the majority of cases, and therefore

their condition belonged to the recurrent type of dislocation occurring in adolescence. Possibly in 2 of these cases, the dislocating patellas were of the congenital type, because both roentgen and operative findings showed marked lateral displacement with the patella firmly fixed in this position. Also, in 1 of the cases in which the condition was congenital, the patella began dislocating at 3½ years of age, and this was the earliest onset in this group. None were of the severe traumatic type.

CAUSATION AND MECHANISM OF DISLOCATION

One of the more interesting features of recurrent dislocation of the patella is that the causation or the actual mechanism of the dislocation

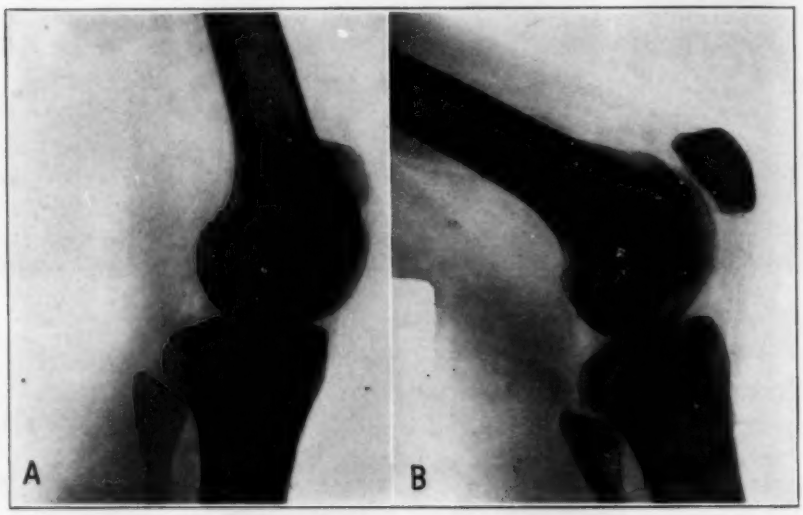

Fig. 2.—Lateral view roentgenograms of a knee: *A*, in extension, showing the patella laterally dislocated; *B*, in flexion, showing the patella in its normal relations to the femoral condyles.

remains obscure. As Gallie and LeMesurier [2] pointed out, in the majority of cases of the adolescent type, there has been nothing in the knee, except perhaps laxity of ligaments, to suggest the cause of the dislocation.

Some of the anatomic features of the normal knee joint are hereinafter reviewed because of their bearing on the mechanism of dislocation.[3]

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2. Gallie, W. E., and LeMesurier, A. B.: Habitual Dislocation of the Patella, J. Bone & Joint Surg. **6**:575-582 (July) 1924.

3. Frazer, J.: Anatomy of the Human Skeleton, ed. 2, London, J. & A. Churchill, 1920. Gray, H.: Anatomy of the Human Body, revised and edited by W. H. Lewis, ed. 23, Philadelphia, Lea & Febiger, 1936. Morris, H.: Morris' Human Anatomy, edited by C. M. Jackson, ed. 8, Philadelphia, P. Blakiston's Son & Company, 1925. Piersol, G. A.: Human Anatomy, ed. 9, revised, Philadelphia, J. B. Lippincott Company, 1936.

1. The deep fascia of the thigh as it descends to the knee blends with the fibrous expansion of the extensor tendon. The fascia is much thinner on the medial side of the patella than on the lateral side and blends much less with the tendon of the vastus medialis muscle than the lateral part of the fascia does with the vastus lateralis muscle. In full extension, only the lower third of the patellar articular surface rests on that of the condyles and its upper two thirds lies on the pad of fat which covers the lower and anterior part of the femur. In extreme flexion, only the upper third of the patella is in contact with the femur, and the lower two thirds rests on the fat pad between it and the tibia.

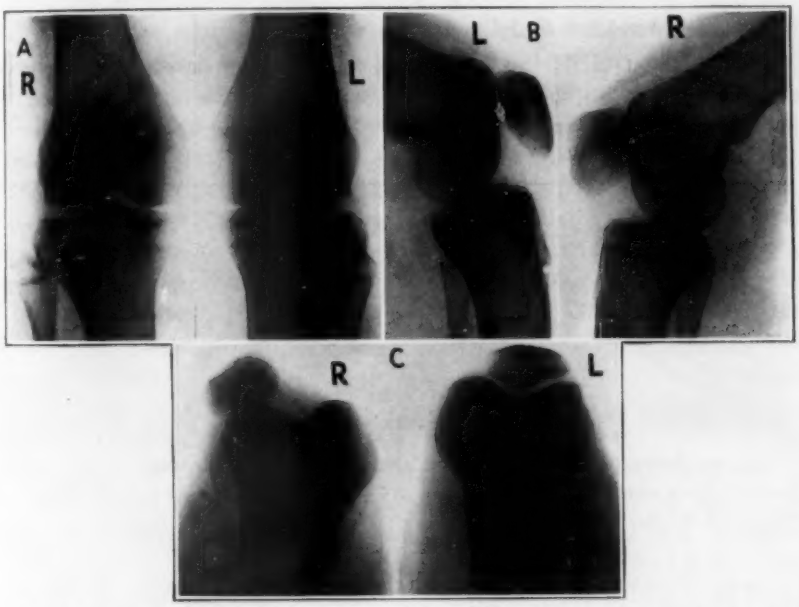

Fig. 3.—Roentgenograms of the knees of a patient with a dislocating right patella and a normal nondislocating left patella: *A*, anteroposterior view of the knees in extension, showing the right patella in its normal position; *B*, lateral view of the knees after the right patella dislocated on flexion; *C*, view showing the right patella slipping off the lateral condyle with the knees in acute flexion. The right and left knees are designated by *R* and *L*, respectively.

2. The patella is held in place as a result of the tension of the quadriceps muscle retaining it in its groove and partly owing to the attachments of the aponeuroses that lie beside it.

3. The vastus lateralis muscle is the largest part of the quadriceps femoris.

4. The greater strength of the vastus lateralis muscle is more than sufficient to overcome the resistance offered by the relatively more exten-

sive insertion of the vastus medialis muscle into the inner margin of the patella.

Thus it may be concluded that in the normal knee the fascia on the medial side of the patella is more easily torn, that the most stable position of the patella is midway between full extension and full flexion and that the components of the quadriceps muscle tending to pull the patella laterally are of greater strength and are acting at better mechanical advantage than those tending to pull the patella medially.

In cases of chronic dislocation of the patella, probably a variety of predisposing causes acting together are responsible for the dislocation. Important predisposing causes, several of which have been mentioned in the literature, are as follows:

Age.—Most of the cases occur at an age when strenuous activities are common. Also, at this age, joint structures have not lost the laxity present during the growing period.

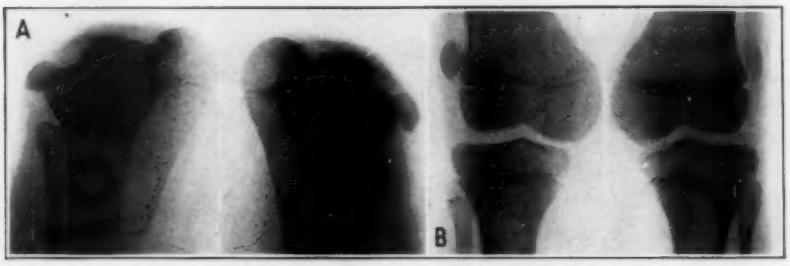

Fig. 4.—Anteroposterior views of bilateral congenital dislocating patella: *A*, in flexion; *B*, in extension. The patellas are permanently dislocated both in flexion and in extension.

Sex.—Normally there is an axial deviation of about 10 degrees between the femur and the tibia. This axial deviation tends to be greater in females because of the wider pelvis; the outward pull of the quadriceps muscle on the patella therefore would be greater than in males. As Winslow [3a] brought out, this outward pull of the quadriceps muscle is probably a factor in causing dislocation. Normally, the quadriceps pulls in the long axis of the femur. The tibia and the femur are at an angle, and the resulting pull is therefore outward as well as upward.

Abnormal Anatomic Factors.—(*a*) Knee Valgus: Knee valgus varies greatly but must be of considerable importance in cases in which the valgus deformity approaches 10 to 15 degrees.

(*b*) Elongated Patellar Tendon: An elongated patellar tendon causes the patella to ride high on the femur.

3a. Winslow, N.: Complete Outward Dislocation of the Patella, Ann. Surg. **79**:415-417 (March) 1924.

(*c*) Tight Fascial Bands: Tight fascial bands on the lateral side of the patella, holding the patella constantly in a more lateral position than normal, have been particularly emphasized as a factor by Ober.[4] It may possibly be of more importance in the congenital type of dislocation in which the patella has developed in a lateral position.

(*d*) Relaxed Medial Capsule: Hauser [5] felt that the trauma sometimes associated with these cases results in the tearing of the medial capsule and the fascia, this allowing the patellar tendon to be displaced laterally. The severity of trauma in many of the cases on which this study is based did not seem sufficient to cause much tearing of the medial capsule or aponeurosis.

(*e*) Aplasia of the Lateral Femoral Condyle: Aplasia of the lateral femoral condyle has frequently been mentioned in the literature as a predisposing cause of dislocation. As already stated, it is difficult to determine the presence of aplasia by physical and roentgen examination. Horwitz [6] found this condition in only 3 of his 20 cases. The importance of this factor has probably been overemphasized.

It was noted in 8 knees that the patella dislocated when the knee was extended from the flexed position. This usually occurred when the knee had reached 165 to 175 degrees of extension. In some knees the patella was in the normal position in full extension, but active contraction of the quadriceps muscle caused the patella to subluxate laterally. Some patellas subluxated laterally when the knee was merely passively extended. As Ober brought out, dislocation of the patella in extension is probably due to the fact that at 165 to 175 degrees extension, the patella begins to lose the support of the lateral condyle, especially if the patellar tendon is elongated. In passing the condyle with the quadriceps pulling at an angle, it is fairly easy for the patella to slip off the lateral side. In other cases it seemed because of knee valgus and abnormal direction of the quadriceps pull, that, as the knee was extended, the patella was pulled up on the lateral condyle or its lateral aspect, instead of into the patellar groove. On further extension, the patella slipped off the lateral condyle. The fact that these patellas slip off laterally in extension during examination does not necessarily explain the disability that patients of this type have. It seems possible that when they are doing something fairly strenuous, such as running or jumping, the patella slips off laterally during extension, and with sudden flexion occurring, the patella is unable

4. Ober, F. R.: Slipping Patella or Recurrent Dislocation of the Patella, J. Bone & Joint Surg. **17**:774-779 (July) 1935.

5. Hauser, E. D. W.: Total Tendon Transplant for Slipping Patella: A New Operation for Recurrent Dislocation of the Patella, Surg., Gynec. & Obst. **66**:199-214 (Feb.) 1938.

6. Horwitz, M. T.: Recurrent or Habitual Dislocation of the Patella: Critical Analysis of Twenty Cases, J. Bone & Joint Surg. **19**:1027-1036 (Oct.) 1937.

to get back onto the trochlear fossa and stays dislocated during flexion also, thus causing considerable disability.

In 4 knees examined, the patellas dislocated laterally at 90 to 110 degrees of flexion. Dislocation in flexion is more common in cases of the congenital type or in those in which a severe degree of valgus exists. There seem to be three possible ways in which the patella is dislocated on flexion of the knee. The patella may slip off laterally during extension and remain in the same position during flexion. Laxity of the medial capsule and aponeurosis favor this. The dislocation may be of the congenital type in which the patella is fixed in the lateral position. When the patella approaches 90 to 100 degrees of flexion, it comes to a more lateral position, its upper portion resting almost wholly against the lateral condyle. In this position a fair degree of outward rotation of the tibia is possible. With considerable valgus present, the outward force acting on the patella tends to make it slip laterally.

Although it has been stated that in most of these cases examination does not usually show any marked deviation from normal, if the clinical, roentgen and operative findings are carefully studied in individual cases, abnormalities are often found. These abnormalities are slight in some cases, it is true, but it apparently does not take much to upset the normal mechanism which stabilizes the patella.

TREATMENT

In this group, the age at operation varied from 4 to 22 years. Most of the operations were done between 12 and 20 years of age. Thirteen patients waited anywhere from six months to eleven years before operation was done. The average period between onset of dislocation and operation was four and three-tenths years.

The operation most commonly performed in treating these patients at the New York Orthopaedic Dispensary and Hospital is transplanting the tibial tubercle with the attached patellar tendon. This operation is similar to the one recently described by Hauser. It has been used at the New York Orthopaedic Dispensary and Hospital since 1932. This procedure was done on 23 knees. In this operation, the tibial tubercle with the attached ligamentum patellae is removed as a block of bone and transplanted into a slot made on the medial side of the tibia, usually 1 or 2 cm. medially, and 1 to 2 cm. distally from its normal insertion. Chromic catgut sutures through the periosteum and the fascia are used to hold the transplanted tubercle in place. If there are tight fascial bands on the lateral side of the patella, they are severed. In some cases the medial capsule is plicated if it is thought to be relaxed.

This operation accomplishes two things:

1. By bringing the patella to a more distal position, the patella gets effective support from the lateral condyle when the knee is in extension.

2. The direction of pull of the quadriceps muscle on the patella is changed so that the component of force tending to pull the patella laterally is eliminated.

In knees in which considerable knock knee is present, the outward pulling force may not be eliminated entirely by the transplant operation and supracondylar osteotomy also will be necessary. This was done in 9 knees.

There was no constancy in the findings reported at operation. An underdeveloped lateral femoral condyle was noted in 4 cases. Usually, this structure is not exposed sufficiently during the transplant operation to determine whether aplasia is present. In 5 cases, tight fascial bands or tight aponeuroses on the lateral side of the patella were reported. However, in 12 cases, it was thought advisable to divide the lateral structures, although whether they were a deforming factor in all of them is not mentioned. In 3 cases, the quadriceps muscle was not in line with the patellar tendon and was therefore exerting an abnormal lateral pull on the patella. This is also more common than noted because a fair degree of knee valgus was present in one third of the cases. In 1 bilateral case, the patellas were found completely dislocated on the side of the lateral femoral condyles. They were held there by tight fascial bands and seemed to have developed in this position.

The synovial membrane of the knee joint was inspected in 2 cases, and it was found thick and congested, with villous hypertrophy. This is a significant finding since in many of these knees osteoarthritis will eventually develop unless the chronic irritating factor of dislocating patellas is corrected by operation.

Postoperative Treatment.—After operation, a long leg cast is applied and kept on for six weeks. At the end of this time, the cast is removed, and a roentgenogram is made to see whether the transplanted block of bone has firmly united in its bed. All of these patients showed firm union in six weeks. Massage and gentle motion are given, and in another week or two the patient is allowed up with crutches, and gradual weight bearing is started. Motion and normal gait return rapidly, and for most patients normal activities are possible at three months.

END RESULTS

End results are classified as excellent, good and poor. A patient with an excellent end result has no patellar slipping, no recurrence of dislocation, no symptoms and no restriction of activity. Anatomically, the patella is in normal position on flexion and extension. Roentgenograms show the absence of arthritic changes, with the patella in a more distal position and riding in the patellar groove.

A good result is one in which the patella does not dislocate, but there may be slight tipping on flexion or extension without symptoms. Roent-

genograms may show slight arthritic lipping without clinical evidence of arthritis, and there may be slight lateral displacement of the patella.

A poor result is one in which the patella dislocates at the time the cast is removed and motion started or which does not dislocate for several months after the operation but subsequently does so.

There were 22 knees with a follow-up period of one to seven years on which the tibial tubercle transplant operation was done. The average follow-up period for this group was three and five-tenths years. Eleven, or 50 per cent, of the knees showed an excellent result; 9, or 40 per cent, showed a good result, and 2 knees, or 10 per cent, showed a poor result. This makes 90 per cent satisfactory results of this type of operation.

One of the poor results was that of a patient who had a growth deficiency at the lower femoral epiphysis. She was still in the growth period, and knee valgus occurred to the same extent as before the supracondylar osteotomy. The other patient with a poor result had slight lateral subluxation of the patella on extension with coarse crepitation on motion. It was thought best to do a retransplant operation on this patient. In spite of the second operation, the patella still subluxated, and at the time of writing, this patient has been readmitted for another operation.

The fascial and capsular structures on the lateral side of the patella were cut in 12 knees at the same time as the tibial tubercle was transplanted. Six of these showed excellent results; 4, good results; 1, poor, and 1 had the retransplant already mentioned.

The medial capsule was reefed or plicated in 8 knees at the time of the transplant operation. In 1, the result was excellent, in 6, good and in 1, poor.

Both plication of the medial capsule and the release of the lateral structures were done in 6 knees. In 1, the result was excellent, in 4, good and in 1, poor.

Nine supracondylar osteotomies were done in patients who had tibial tubercle transplants. The amount of genu valgum varied between 10 and 20 degrees, most of the knees having 15 degrees of valgus. Five of these patients had supracondylar osteotomies before the transplant, and the osteotomy was not enough to cure the dislocation. Of the 5, 2 were immediately cured by the transplant. One had a second osteotomy soon after the transplant because valgus had partially recurred and because it was found at operation that the patella was not stable in flexion even after the tibial tubercle has been transplanted. One (in whom the condition was due to a growth disturbance) had a transplant operation which failed to stabilize the patella. A second osteotomy was done, but valgus recurred, and the patella still dislocated.

One patient, in whom the condition was bilateral, had supracondylar osteotomies just before the transplant operation; thus the value of the

osteotomies in this case is not known. One other patient, whose condition also was bilateral, had osteotomies one year after transplants, not because of dislocation but because it was thought that osteotomies would give a more mechanically sound joint.

Of the 9 cases in which supracondylar osteotomies and transplants were done, in 2, the results were excellent, in 5, good and in 2, poor. On the other hand, there were 10 knees which had transplants alone without osteotomy; all of these showed excellent results. None of those which had transplants alone had an appreciable amount of valgus. In knees with severe knock knee deformity of 15 to 20 degrees, it is important to correct the valgus by supracondylar osteotomy before doing the transplant operation. In 3 patients, supracondylar osteotomy failed to stabilize the patella because of the recurrence of knock knee. Subsequent tibial tubercle transplants were not adequate to prevent dislocation until a revision of the osteotomy was done and the knock knee corrected. In the average patient with recurrent dislocation of the patella, with only moderate genu valgum (5 to 10 degrees), the transplant operation can be done alone with the expectation that no further operation will be necessary.

In 1 case in which the condition was bilateral, supracondylar osteotomy alone was done. Both knees showed a good result years later. There was 10 degrees valgus deformity before operation.

Plication of the medial capsule alone was done in 2 knees. Six years later, 1 knee showed a good functional result, the patella subluxating slightly to 160 degrees extension. In the other case, a transplant of the tibial tubercle was required one and one-half years later because of the recurrence of dislocation.

CONCLUSIONS

The causation of chronic recurrent dislocation of the patella in adolescence is obscure but probably involves a combination of factors acting together on a certain age group, made up chiefly of the female sex.

In many instances, chronic recurrent dislocation of the patella is not much disabling but nevertheless should be treated by operation to prevent the early onset of osteoarthritis.

Operative treatment by means of the tibial tubercle transplant operation is not technically difficult and is satisfactory. This should be combined with plication of the medial capsule and release of tight fascial bands laterally, when necessary.

In the more severe types of deformity, with considerable genu valgum, both supracondylar osteotomy and tibial tubercle transplant will have to be done. The complete correction of valgus deformity should be emphasized.

TUMORS OF TENDON SHEATHS

HERMAN CHARACHE, M.D.
BROOKLYN

Tumors of tendon sheaths, excluding ganglion, are rare. Buxton,[1] whose work on tendon sheath tumors is so frequently quoted, stated:

> . . . This structure [tendon sheath] is a specialized part of connective tissue and is therefore subject to the same neoplasms as other connective tissue. Such neoplasms are not uncommon. Therefore one searches for some reason why tendon sheaths should be so immune from tumor formation, and it is very difficult to find any facts bearing on this point.

According to Canavero,[2] only 1 or 2 cases are found in every 2,000 hospital or clinic admissions. At the Brooklyn Cancer Institute, the Cumberland Hospital and the Jewish Sanitarium and Hospital for Chronic Diseases, among 10,500 hospital admissions and 157,000 clinic admissions in the past ten years, only 5 cases of tumors of the tendon sheaths were found. And yet these 5 cases all occurred in the year 1939-1940. Are these tumors becoming more prevalent than before? One can only tell if more cases are reported in the literature.

Because of the rarity of these tumors and the lack of information on the subject in modern textbooks, a complete review of the literature was made, and the following classification of tumors of tendon sheaths was evolved:

Benign

1. Ganglion
2. Xanthomatous giant cell tumor
3. Lipoma
4. Hemangioma
5. Lymphangioma
6. Fibroma
7. Osteochondroma

Malignant

1. Synovioma
2. Spindle cell sarcoma
3. Chondrosarcoma

BENIGN TUMORS OF TENDON SHEATHS

Ganglion.—Ganglion is a benign cystic neoplasm containing mucinous or gelatinous material which is the product of collagenic degener-

1. Buxton, S. J.: Brit. J. Surg. **10**:469, 1923.
2. Canavero, M.: Policlinico (sez. chir.) **41**:341, 1934.

ation. It arises from the connective tissue of the joint capsule or the tendon sheath. This view was first brought out by Clarke [3] in 1908, was accepted by many writers and was included in Dean Lewis' [4] report of 40 cases of ganglion in 1934. Occasionally, ganglion may arise from the joint capsule and invade the tendon sheath by contiguity, without communicating with either cavity.

The tumor is most prevalent during adolescence and early adult life. Some cases have been reported in children (Lewis). Trauma is considered a predisposing cause in the formation of ganglion. In 50 cases reported by De Orsay, Mecray and Ferguson,[5] 19 (38 per cent) were associated with trauma. The dorsum of the wrist is the most frequent site of formation. Other sites, in order of frequency, are: the volar surface of the wrist and the fingers, the dorsum of the foot and the popliteal region. The outstanding symptom is the presence of a tumor. While pain is not a dominant symptom, the patient may complain of weakness and pain on grasping or lifting. Most ganglions removed in the operating room confirm the clinical diagnosis because the diagnosis of any other tumor is seldom made. Almost all tumors in the wrist are diagnosed as ganglion.

The treatment of choice is complete surgical excision of the ganglion, including the deep ramifications between and around the adjoining tendon sheaths and joint ligaments, preferably in the operating room. Only a small percentage lend themselves to safe removal at the clinic dressing table.

Considering the various tumors found in tendon sheaths, one can only mention the method of striking the tumor with a heavy object in order to condemn it. Surely one would not recommend this treatment for a tumor of unknown type in another part of the body. True, ganglion is the most commonly found tumor in this region, but tumors of other types also may be found, as will be discussed in this paper. The surgical axiom, "See what you do, and do what you see," applies to any part of the human body and extends to the treatment of tumors of the tendon sheaths.

The treatment of ganglion by the injection of sclerosing solutions has been tried with some success in isolated instances.

Sixty cases of ganglion were recorded at the Cumberland Hospital from 1931 to 1941. In 54 cases (90 per cent), the patients were female; in 6, they were males. The oldest patient was a 68 year old man; the youngest was a 7 year old girl. Two cases occurred in the first decade of life; 19, in the second; 22, in the third; 8, in the fourth; 7, in the fifth, and 2, in the seventh. Forty-six (77 per cent) occurred on the

3. Clarke, W. C.: Surg., Gynec. & Obst. **7**:56, 1908.

4. Lewis, D.: Surg., Gynec. & Obst. **59**:344, 1934.

5. De Orsay, R. H.; Mecray, P. M., Jr., and Ferguson, L. K.: Am. J. Surg. **36**:313, 1937.

dorsal surface of the wrist, and 5 (8 per cent) on the volar surface. Six (10 per cent) occurred in the region of the foot; 2 (3 per cent), in the popliteal region, and 1 (1 per cent), in the finger. The size varied from that of a pea to that of a walnut. The duration of the disease varied from four months to ten years, with an average of twenty-one months. Trauma as a predisposing cause was found in 8 cases (13 per cent); in 5 of these the trauma was at the site of healed fractures. The right and the left extremities were equally involved. In 2 cases, the condition was bilateral (wrist). Only 10 patients (17 per cent) complained of pain.

Xanthomatous Giant Cell Tumor.—A soft tissue tumor of the tendon sheath, varying in size from that of a pea to that of a hen's egg, yellowish brown, lobulated, surrounded by a capsule and composed of polyhedral or spindle cells, dense connective tissue, giant cells, large vesicular lipoid cells, pigment of hemosiderin and, occasionally, cholesterol crystals, fibrocartilage or even bone trabeculae—this type of tumor is often referred to as giant cell sarcoma, endothelioma, myeloma, xanthoma and granuloma. Little wonder then that the average reader on this subject is so confused as to the identity of this type of tumor. Geschickter and Copeland,[6] and Lewis, who made a thorough study of the literature on this subject and studied 52 cases of their own in the laboratories of Johns Hopkins Hospital, Baltimore, restricted the name "giant cell tumor" or "xanthomatous giant cell tumor" to this type of growth of the tendon sheath.

Next to ganglion, the giant cell tumor is the most common growth found in the tendon sheath. In more than 50 per cent of the cases, it is located in the tendon sheaths of the fingers at the metacarpophalangeal or interphalangeal joint near the tendinous insertion or next to a sesamoid bone. Next in frequency are the palm, the wrist, the toes, the ankle, the arms and the legs. In 32 of the 50 cases reported by Lewis, the growth was located in the tendon sheaths of the fingers. In the remainder, it was elsewhere in the hand or about the foot and the ankle. Based on a careful histologic study, Geschickter and Copeland and Lewis all agreed that there is a definite relation between this tumor and the sesamoid bones.

Diagnosis is difficult since the symptoms and signs are not characteristic of this tumor alone. Roentgen examination may reveal some fibrocartilage and bone trabeculae in certain cases only. Xanthelasma of the skin in other parts of the body and hypercholesteremia may be found in some cases.[7] The treatment is complete excision. The prog-

6. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, New York, American Journal of Cancer, 1936, p. 736.

7. Ollerenshaw, R.: Brit. J. Surg. **10**:466, 1922.

nosis is good; recurrence is rare. The tumor, according to Ewing[8] and many others, does not metastasize. However, Ragins[9] found 6 cases in the literature in which bone was invaded. Three additional cases were reported by Geschickter and Lewis.[10]

Lipoma of Tendon Sheaths.—Lipoma of the tendon sheaths is rare. In 1924, White[11] emphasized the "extreme rarity of this condition, as evidenced by the small number of cases reported and by the fact that no surgeon has reported more than one case of his own observation." In 1922, Strauss[12] found only 18 cases reported in the literature and added a case of his own. His study and complete analysis of these cases contributed a great deal toward the study of this subject. In 1931, Straus[13] found 34 cases reported and added 1 of his own. Two cases were reported by Geschickter and Lewis[10] in 1934. One case was reported by each of the following authors: Valdoni (1931),[14] Canavero (1934),[2] Periset (1938)[15] and Jadevaia (1940).[16] These represent a total of 41 cases. I wish to add 2 additional cases, making a total of 43 cases.

Lipoma of the tendon sheaths occurs in two forms: the simple lipoma, which often occurs symmetrically in both hands and usually involves a single tendon sheath, and the arborescent type, which is analagous to the fat of the appendices epiploicae and which because of its arborescence involves more than one tendon sheath. The latter is the more prevalent. Histologically, the arborescent type contains more fibrous tissue and is more vascular but is otherwise indistinguishable from any other lipoma.

The extensor tendons of the hands and the feet are most commonly involved. The former are twice as frequently involved as the latter. The symptoms vary with the size of the tumor; the larger the tumor, the greater the pressure symptoms along the neighboring nerves and the greater the interference with the movements of the tendons. Tingling, numbness and stiffness of the fingers are often complained of. The majority of the patients are male and between the ages of 15 and 30.

Diagnosis is difficult; in only 3 cases has the diagnosis been made before operation. The tumor is soft, sometimes giving a strong suggestion of fluctuation. It may become firmer in consistency when it is chilled with an ice bag. This has been employed as a diagnostic aid in

8. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 282.
9. Ragins, A. B.: Ann. Surg. **93**:683, 1931.
10. Geschickter, C. F., and Lewis, D.: Am. J. Cancer **22**:96, 1934.
11. White, J. R.: Surg., Gynec. & Obst. **38**:489, 1924.
12. Strauss, A.: Surg., Gynec. & Obst. **35**:161, 1922.
13. Straus, F. H.: Ann. Surg. **94**:269, 1931.
14. Valdoni, P.: Chir. d. org. di movimento **15**:509, 1931.
15. Periset, P.: Chir. d. org. di movimento **24**:78, 1938.
16. Jadevaia, F.: Gior. di med. mil. **88**:137, 1940.

a number of cases. Some roentgenologists are able to differentiate lipoma from other soft tissue shadows.

Treatment is complete surgical removal. In most cases part of the tendon sheath has to be removed with the tumor.

The prognosis is good. Recurrence seldom takes place when the tumor is completely removed. The arborescent type is more likely to recur, because one or more of its ramifications may be left behind.

Hemangioma of the Tendon Sheath.—Hemangiomas in general are relatively common tumors; however, hemangioma of the tendon sheaths is rare. Burman and Milgram [17] found but 10 cases reported in the literature up to 1930 and added 6 of their own. In 1937, Harkins [18] found 24 cases, including 1 of his own. Another case was reported by Piccagli [19] in 1939. To this number I wish to add an additional case, making a total of 26 up to the time of writing.

Although hemangiomatous tumors are considered by Ewing and others to be of congenital origin, in only 3 of the reported cases of hemangioma of the tendon sheath was the growth known to have been present at birth. In more than half the cases there has been a history of trauma previous to noticing the tumor. However, although trauma of the extremities is so common, hemangioma develops in few cases. Trauma is much more frequent in male than in female patients, yet hemangioma of the tendon sheaths is twice as prevalent in female as in male patients. The condition usually occurs during early adult life. The upper extremity is involved twice as frequently as the lower. The sites in the upper and the lower extremities in the order of frequency are as follows: the forearm, the wrist, the leg, the hand, the foot and the thigh.

Pain and the presence of a tumor are the only symptoms which bring the patient to the hospital. Pain is usually due to angiolithic concretions or nerve pressure. The median or the radial nerve is usually involved; less frequently, the ulnar nerve. The pain is aggravated during complicated movements of the fingers, such as piano playing, and with the increase in size of the tumor. Occasionally there will be no symptoms at all except the presence of the tumor, and the patient will wait many years before coming for treatment. The longest period between the appearance of the tumor and reporting for treatment was seventeen years; the average was four years.

The tumor varies in size and shape. It may be the size of a hazelnut or the size of an orange. It may be spheroid or spindle shape. It decreases in size when the extremity is elevated or when it is compressed with the fingers. It increases in size in the dependent position

17. Burman, M. S., and Milgram, J. E.: Surg., Gynec. & Obst. **50**:397, 1930.

18. Harkins, N.: Hemangioma of Tendon or Tendon Sheath, Arch. Surg. **34**: 12 (Jan.) 1937.

19. Piccagli, G.: Chir. d. org. di movimento **24**:533, 1939.

or on circular compression of the limb. The overlying skin is freely movable and takes a deeper purplish hue during the dependent position or circular compression. The tumor moves with the movement of the involved tendon. Occasionally one can palpate the angiolithic concretions within the tumor. The tumor itself has a cystic feel. The concretions show up well on roentgen examination.

Complete surgical excision is the treatment of choice, and no other treatment can be substituted for it. The prognosis of angioma of tendon sheaths is good. The rarity of recurrence, of functional disturbance or of malignant transformation bespeaks its results.

Lymphangioma.—Only 5 cases of lymphangioma of the tendon sheath were found in the literature by Harkins in 1937. There has been no other case reported up to the time of writing. The clinical course differs little from that of hemangioma.

Fibroma.—There have been 51 cases of fibroma of the tendon and the tendon sheaths reported in the literature up to the time of writing. Janik [20] found 19 cases reported in the literature before 1927. Torchiana [21] and dal Pozzo [22] each reported a case in 1931. Thirty cases were reported from Johns Hopkins Hospital by Geschickter and Copeland [6] in 1934. In the series of Geschickter and Copeland, the majority of the patients were between 10 and 25 years of age. The next most common age group was between 35 and 45. The greater part of the lesions were in the upper extremity.

Fibroma of the tendon sheaths is a small circumscribed firm nodule, not adherent to the skin but intimately attached to the tendon sheath, simulating subcutaneous fibroma in any other part of the body. In some instances, it is associated with multiple neurofibromatosis, as observed by Brunschwig.[23] It does not recur after complete excision. Because of its circumscribed nature, it lends itself to complete excision more readily than any other tumors in this region. Part of the tendon sheath has to be excised with the tumor.

Osteochondroma.—Osteochondroma of the tendon sheath usually arises near the osseous insertion of the tendon, where precartilaginous tissue normally exists. Histologically, it does not differ from similar lesions in other parts of the body and is subject to malignant transformation. It varies in size from that of a cherry to that of a hen's egg, and interferes with the movements of the tendons, resulting in pain. The majority of cases have occurred during adult life. The hands and the feet are most commonly involved. The treatment is complete excision. Part of the tendon sheath and, in some instances,

20. Janik, A.: Ann. Surg. **85**:897, 1927.
21. Torchiana, L.: Arch. ital. di chir. **28**:436, 1931.
22. dal Pozzo, C.: Cancro **2**:116, 1931.
23. Brunschwig, A.: Tumors of the Hands and Feet, St. Louis, C. V. Mosby Company, 1939, p. 109.

even part of the tendon may have to be sacrificed. Twenty-two cases have been reported in the literature up to the time of writing; Geschickter and Copeland [24] found 15 cases reported and added 7 additional cases.

MALIGNANT TUMORS OF TENDON SHEATHS

Synovioma.—Synovial tumors are rare; still rarer are synovial tumors of the tendon sheath. In 1937, Coley and Pierson [25] found only 20 cases of synovial tumors reported in the literature. They reported 15 additional cases from the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, from 1900 to 1937, only 1 of which was of possible tendon sheath origin. A year later, Berger [26] reported 5 additional cases and analyzed the cases already reported. He concluded as follows: "Our own cases included, there are actually 23 cases in all presenting specific synovial factors, of which 11 are articular, 9 in bursae, and 3 in tendon sheaths." The 15 cases of Coley and Pierson were not included in this report. In the same year, Jönsson [27] reported 14 cases of synovial tumors from Radiumhemmet in Stockholm, Sweden, 6 of which occurred in tendon sheaths. One case of synovioma was reported by Hutchison and Kling [28] in 1940, and 16 cases were reported by DeSanto, Tennant and Rosahn in 1941 [29]; 2 of these were of tendon sheath origin. This makes a total of 69 cases of synovial tumors, of which 12 (17 per cent) originated in tendon sheaths.

Jönsson divided synovial tumors into synovialoma and synovial fibrosarcoma. The former has a greater tendency to pulmonary metastasis, involves the regional lymph glands and is radiosensitive. The latter has a relatively more benign course, almost never involves the regional lymph glands, does not tend to pulmonary metastasis so commonly and is radioresistant.

Histologically, synovialoma is composed of spindle cells, polygonal and endothelial cells and small or large cystic cavities lined with cuboid or endothelial cells. Occasionally, epithelial cells group themselves to enclose a lumen, simulating a gland structure, the so-called pseudo-alveoli.

Synovial fibrosarcoma is less cellular and is composed of a greater amount of fibrous tissue and spindle cells, the nuclei of which are larger and narrower than in synovialoma.

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24. Geschickter and Copeland,[6] p. 733.
25. Coley, B. L., and Pierson, J. C.: Surgery **1**:113, 1937.
26. Berger, L.: Am. J. Cancer **34**:501, 1938.
27. Jönsson, G.: Acta radiol., 1938, supp. 36, p. 1.
28. Hutchison, C., and Kling, D. H.: Am. J. Cancer **40**:78, 1940.
29. DeSanto, D. A.; Tennant, R., and Rosahn, P. D.: Surg., Gynec. & Obst. **72**:951, 1941.

Grossly, synovial tumors are of soft consistency, even fluctuating at times, although some are reported as firm. They vary in size from that of a walnut to that of an orange. In the larger tumors, the overlying skin may be infiltrated and even ulcerated. The superficial veins are markedly dilated. The cut surface is grayish white or brownish, showing cystlike cavities containing brownish or yellowish fluid. In describing the gross appearance of the tumors, Jönsson stated: "It is striking how the operator received more the impression of a chronic inflammatory process than a tumor."

The clinical course of synovioma is the same, whether it occurs in the joint capsule, the tendon sheath or the bursae. The diagnosis is most difficult. The pathologist is usually the one who makes the diagnosis after removal of the tumor, and this he does after a great deal of deliberation and study. Subjective symptoms are few. The patient first notices a swelling. Pain, weakness and a tingling sensation of the fingers or the toes are later manifestations. The tumor itself is not characteristic of synovioma alone, even under the most scrupulous clinical study. Roentgen examination is of no avail in helping the diagnosis; however, it may rule out other types of tumor. The wrist, the hand, the ankle and the foot are the most common sites of the tumor. Male and female patients are equally affected, and the tumor is most prevalent between the ages of 20 and 50.

Early high amputation is the treatment of choice. Berger quoted Sabrazes as follows:

> . . . It is amputation which should impress itself from the first examination. The family, the physician, the surgeon, the pathologist hesitate proposing such a sacrifice in the presence of a tumor which seems to be so slightly malignant in the first stage of its development. Later one is forced to this intervention; one undertakes it, alas, too late.

Coley and Pierson stated that any operable tumor which by its location suggests the probability or even the possibility of synovioma should be removed by wide excision followed by roentgen therapy after the diagnosis is confirmed by the pathologist. In the event of recurrence, they recommended prompt amputation, provided the lungs are free from metastasis. Although they agreed that the tumor is not radiosensitive, they recommended radiation therapy for postoperative and nonoperative treatment.

The prognosis of synovioma, as given by Coley and Pierson, is 20 per cent five year cures and 40 per cent three year survivals.

Spindle Cell Sarcoma.—Spindle cell sarcoma is the rarest of all tendon sheath tumors. Geschickter and Copeland [30] could find but 5 cases at the laboratories of Johns Hopkins Hospital. In all of them the patients were children or young adults. In 2, the tendon of the

30. Geschickter and Copeland,[6] p. 738.

quadriceps femoris muscle was involved; in 1, achilles tendon; in 1, the region anterior to the ankle joint, and in the fifth, the region above the phalanx of the toe. In all of them there was recurrence after primary excision. Cooperman [31] reported a case of spindle cell sarcoma of the right foot in a woman of 22 involving the tendon sheath of flexor brevis digitorum. An additional case is reported hereinafter from the Brooklyn Cancer Institute in which the growth involved the region of the achilles tendon.

Chondrosarcoma.—An equally rare tumor of the tendon sheath is chondrosarcoma. Two cases were reported by Geschickter and Copeland.[24] They cited 1 case of Jones [32] and another of Kienböck.[33] A fifth case was reported by Buxton and a sixth by Janik. In 2 of the cases, the growth occurred at the achilles tendon.

REPORT OF CASES

Benign Tumors of Tendon Sheaths

CASE 1 (Lipoma).—A. S., a white woman 40 years of age, was admitted to the Cumberland Hospital on April 14, 1940, complaining of a swelling over the left wrist. About two years previous to admission, she had fallen in a bathtub and injured the left forearm. A week later she noticed the swelling. For the next two years, she could not use her hand effectively without experiencing a certain amount of pain, particularly over the radial side of the hand. The hand would "fall asleep" at frequent intervals, especially the thumb and the index finger. In the last two weeks the tumor greatly increased in size, and the pain was aggravated, radiating from the radial side of the hand to the elbow. The past history and the familial history were otherwise uneventful.

Physical examination revealed a well developed white woman, not acutely or chronically ill. The temperature, pulse and respiration rates were normal; the blood pressure was 190 systolic and 110 diastolic. An irregular firm cystic mass was found over the dorsal surface of the lower third of the forearm and measured 6 by 2 cm. The tumor appeared to be deeply situated and fixed to the underlying structures. The overlying skin was of normal appearance and freely movable. There was no limitation of movements of the fingers, but the patient experienced pain over the tumor in the forearm when she opened or closed her hand. The rest of the physical examination did not reveal any pathologic condition. The blood count was within normal limits; the urine was normal, and the Wassermann test of the blood was negative.

The patient was scheduled for removal of the tumor under local anesthesia. An incision was made over the mass. A tumor presented itself, pushing the muscle in front of it. On careful dull dissection, a spindle-shaped encapsulated fatty tumor, 7 by 2 cm., was found underneath the muscle fibers. The tumor was firmly attached to the sheath of the extensor digitorum communis muscles. The tumor was removed, and the wound was closed in the usual manner.

The pathologic report was lipoma. The patient made an uneventful recovery.

CASE 2 (Lipoma).—R. R., a boy aged 15, was admitted to the Brooklyn Cancer Institute on March 9, 1940, complaining of a swelling of the left hand.

31. Cooperman, M. B.: J. Bone & Joint Surg. **14**:173, 1932.
32. Jones, H. T.: J. Bone & Joint Surg. **6**:407, 1924.
33. Kienböck, A.: Röntgenpraxis **3**:406, 1931.

About seven years before, he had noticed a small painless lump on the dorsum of the left hand. The tumor grew progressively larger, reaching the size and shape of a pear.

Examination revealed a pear-shaped tumor over the dorsum of the wrist and the web between the thumb and the index finger, freely movable on extension and flexion of the hand. The tumor was soft and cystic and not attached to the

Fig. 1 (case 2).—Photomicrograph of arborescent lipoma of tendon sheath.

skin or underlying structures and measured 7.5 by 5 cm. The overlying skin was slightly reddened but not inflamed. Roentgen examination of the wrist did not reveal any pathologic condition of the bone or any opaque substance.

In the operating room under local anesthesia an elliptic incision was made over the tumor. A lobulated yellow elastic mass was found attached to the sheath of the tendons of the extensor pollicis longus and extensor digitorum communis muscles. It completely filled the space between the two tendons and

bulged to the surface. The tumor was removed without difficulty, and the wound was closed in the usual manner.

The pathologic report was lipoma (fig. 1).

CASE 3 (Hemangioma).—G. DeM., a 13 year old white boy, was admitted to Cumberland Hospital on March 4, 1939, complaining of a swelling of the left forearm. The swelling was first noticed at the age of 3. At that time it was

Fig. 2 (case 3).—Photomicrograph of hemangioma of tendon sheath.

the size of a cherry but it grew progressively larger. The swelling would "go up and down" the forearm as the hand was opened and closed. It did not interfere with the boy's activities and was painless.

Examination revealed a soft cystic ill defined mass on the ulnar surface of the lower third of the left forearm, which measured 3 cm. in diameter. When the forearm was held up, the tumor diminished in size. The tumor mass moved with the movements of the fingers.

In the operating room with the patient under local anesthesia an incision was made over the mass. A multilobulated purplish blue cystic tumor, measuring

about 2.5 by 3 cm., was found between the flexor pollicis longus muscle and the tendon of the brachioradialis muscle. When the tumor was removed by dull and sharp dissection from the tendon sheath of the brachioradialis muscle, to which it was intimately attached, part of the tendon sheath had to be removed with it. It contained several small dark red nodules (phleboliths). The pathologic report was cavernous angioma (fig. 2). The patient made an uneventful recovery.

CASE 4 (Fibroma).—O. T., a white woman aged 55, was admitted to the Jewish Sanitarium and Hospital for Chronic Diseases on Oct. 16, 1939, with a

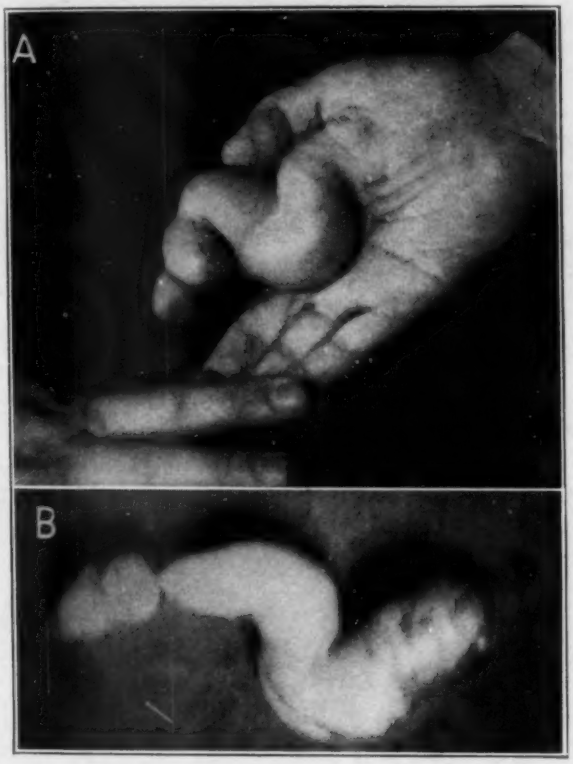

Fig. 3 (case 4).—Fibroma of the tendon sheath: *A*, before operation; *B*, gross specimen removed at operation.

diagnosis of hypertensive cardiovalvulart disease and right hemiplegia. On physical examination it was disclosed that the patient had a tumor of the right index finger. The patient stated that eighteen years before she had noticed a small tumor of the distal phalanx of the right index finger, which grew slowly toward the palm. It had grown more rapidly during the last three years and prevented her from grasping objects. She experienced also some pain from time to time.

Examination revealed an irregular sausage-shaped tumor along the flexor tendon of the right index finger from the distal phalanx to the hypothenar eminence (fig. 3). The tumor was of a soft consistency, not attached to the skin, slightly

movable and moved with the extension and flexion of the index finger. Roentgen examination revealed no abnormalities. A provisional diagnosis of xanthomatous giant cell tumor was made.

Operation was performed with the patient under local anesthesia. The tumor involved the tendon sheath of the index finger, as previously outlined. It was

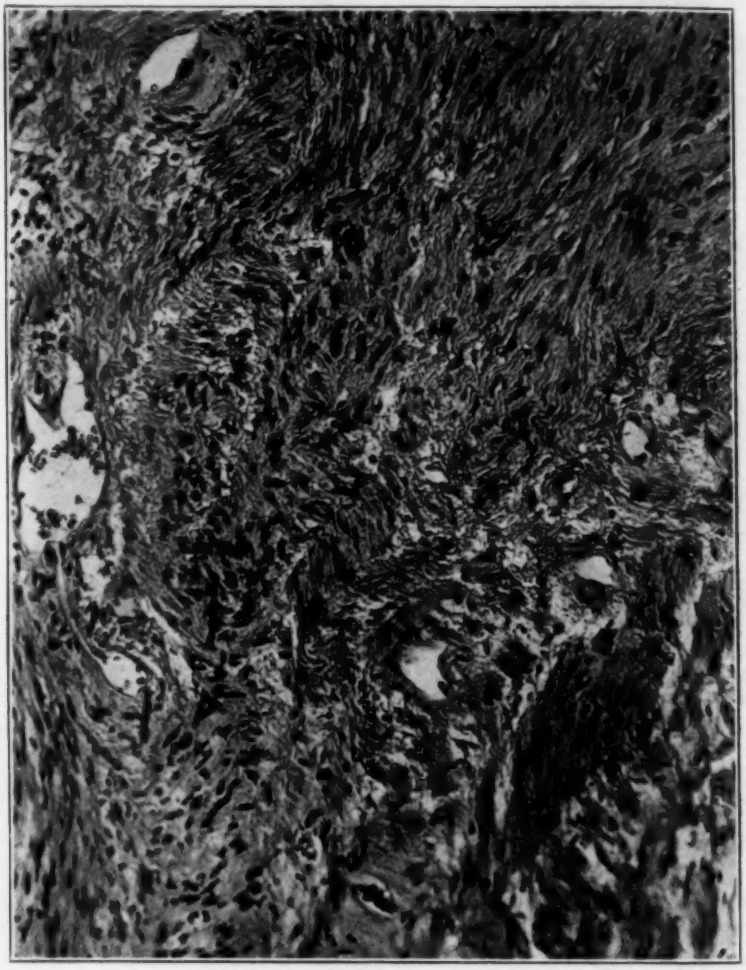

Fig. 4 (case 4).—Photomicrograph of fibroma of tendon sheath.

removed without difficulty, leaving the white glistening tendon bare of its sheath. The patient made an uneventful recovery. The pathologic report was fibroma (figs. 3*B* and 4).

Malignant Tumors of Tendon Sheaths

CASE 5 (Spindle Cell Sarcoma).—D. M., a white man aged 20, was admitted to the Brooklyn Cancer Institute on April 11, 1940, for radiation therapy

following excision of a tumor of the right heel in another hospital. Three years previous to admission to that hospital, he had noticed a small lump on the inner side of the right heel. It did not give him any trouble until shortly before admis-

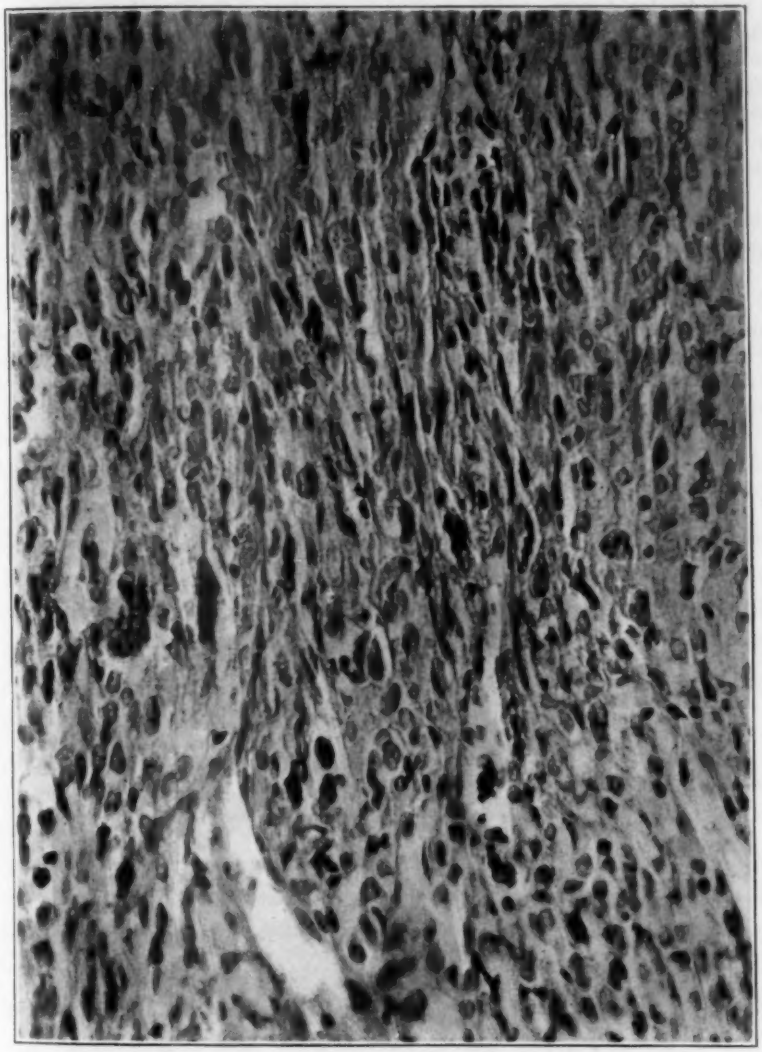

Fig. 5 (case 5).—Photomicrograph of spindle cell sarcoma.

sion, when he noticed that the swelling had increased in size and was associated with pain on walking. He was unable to wear a shoe on that foot because of the pain. On March 30, 1939, he was admitted to the hospital, where a tumor the size of an orange was found in the inner and posterior side of the right heel in the region of the achilles tendon. The tumor was firm and fixed to the under-

lying tissue. The center was friable and necrotic. The tumor was excised locally. The pathologic report, which was later confirmed by the department of pathology of the Brooklyn Cancer Institute, was spindle cell sarcoma (fig. 5).

On admission to the Brooklyn Cancer Institute, the patient was found to be a well developed young man, not acutely or chronically ill. A partially healed infected scar, measuring 6 by 8 cm., was found on the medial surface of the right heel. The surrounding area was indurated. The inguinal glands were not enlarged. Roentgen examination of the leg, the foot and the lungs showed no evidence of pathologic condition. The Wassermann test of the blood was negative; the blood count and blood chemistry were within normal limits. The urine was normal.

After roentgen therapy, the wound remained healed until February 1940, when it broke down. The ulcerated area was excised, and a full thickness graft was applied. The excised tissue contained malignant cells showing radiation changes. The wound healed, and the patient was free from any symptoms when he was discharged on July 17. He returned to the hospital on Jan. 20, 1941 complaining of pain in the chest and hemoptysis. At this time, roentgen examination of the chest revealed pulmonary metastasis and large pleural effusion. Examination of the aspirated fluid showed the presence of sarcomatous cells. The patient died on February 18. Consent for autopsy was not obtained.

SUMMARY

Tumors of tendon sheaths are rare.

A critical study and a classification are made of the cases reported in the literature.

Sixty-five new cases are reported, 60 of ganglion, 2 of lipoma, 1 of hemangioma, 1 of fibroma and 1 of spindle cell sarcoma.

END RESULTS OF A NEW INCISION FOR FELON (INFECTION OF THE ANTERIOR SPACE)

JEROME J. WEINER, M.D.
NEW YORK

On incising the anterior closed space, besides the external signs of swelling, redness and tenderness together with a point of entry and throbbing pain (which is worse at night), one finds edema and swelling of the perpendicular connective tissue fibers. Pus is interspersed between the fibers, and the tuft of the phalanx shows evidences of softening. In cases of advanced infection, the tuft and part of the shaft of the phalanx are destroyed, and in cases in which the infection has reached a late stage, the entire phalanx is necrotic. In the latter type of case, an attempt should be made to preserve the base of the phalanx since it possesses regenerative powers.

Early sections of the distal portion of the phalanx reveal polymorphonuclear exudation into the marrow. Roentgen examination at this stage does not reveal any evidences of the destruction of bone. This is natural, because osteomyelitis is seen in the roentgenogram only after there has been a sufficient accumulation of microscopic areas of inflammation and necrosis to produce a gross lesion.

Figure 2 is a photomicrograph of a section from the finger of a 13 year old boy which was punctured forty-eight hours prior to operation. It reveals fibrous tissue periosteum about the cortex of the bone, and in some areas the bony spicules reveal a diminution in osteocytes. The marrow shows fat cells surrounded by dense masses of polymorphonuclear cells and round cells.

Figure 3 is a photomicrograph of a section of the finger of a 20 year old male patient who gave a history of having injured his finger two weeks before operation. This section reveals the disappearance of the marrow fat cells in addition to the changes found in figure 2.

Figure 4 is a photomicrograph of a section of the finger of a 23 year old man whose injury occurred three weeks before operation. This section shows production of granulation tissue consisting of new capillaries, fibroblasts, lymphocytic infiltration and deposition of collagen. This is found within the bone marrow.

Figure 5 is a sagittal section of a normal thumb. It demonstrates clearly the density of the connective tissue trabeculae in the vicinity of the tuft.[1] Division of these fibers is essential, if one is desirous of obtaining adequate drainage of infection of the anterior space. If the connective tissue fibers are necrotic, their removal together with the tuft of the distal phalanx will prevent further invasion of the bone and thus shorten the healing period. Neither the median incision nor the lateral

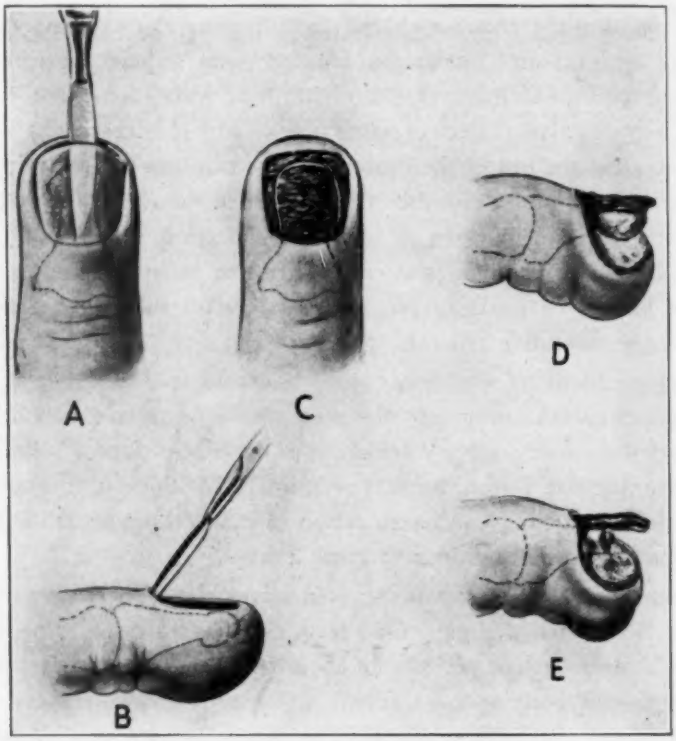

Fig. 1.—Diagram of the incision for infections of the anterior space showing: *A* and *B*, the method of detaching the nail from its bed, matrix and skin attachments; *C* and *D*, the inverted U-shaped incision carried down close to the tuft and to the distal portion of the terminal phalanx; *E*, the ample exposure obtained and the resultant gross lesion following removal of the tuft, if it is found to be involved.

hockey stick incisions divide the perpendicular fibers completely. The result is that these fibers form a thick plug of necrotic tissue which

1. Brickel, A. C. J.: Surgical Treatment of Hand and Forearm Infections, St. Louis, C. V. Mosby Company, 1939.

interferes with drainage and dams back the infection into the haversian canals and the bone cells. Roentgenograms taken a few weeks after incision invariably show evidences of bone destruction. It is only after the plug of necrotic tissue is removed and the diseased bone extrudes itself that healing takes place. This process requires a long period of treatment. The fish mouth incision completely divides the connective

Fig. 2.—Photomicrograph showing fibrous tissue periosteum about the cortex of the bone. In some areas the bony spicules reveal a diminution in osteocytes. The marrow shows fat cells surrounded by dense masses of polymorphonuclear cells and round cells.

tissue trabeculae and gives adequate drainage. However, it leaves an ugly scar with an area of hyperesthesia above and an area of anesthesia below it.[2] Figure 6 shows the end results of fish mouth incisions.

2. Mason, M. L.: Minnesota Med. **20**:485 (Aug.) 1937. Koch, S. L.: Pennsylvania M. J. **40**:597 (May) 1937.

Figures 7 and 8 (cases 1 and 2) show instances in which the tuft was removed together with the necrotic connective tissue fibers.

Figures 9 and 10 (cases 3 and 4) are composed of roentgenograms taken in cases in which the tuft was left intact.

Fig. 3.—Photomicrograph showing the disappearance of the marrow fat cells in addition to the changes shown in figure 1.

The healing period in cases 1 and 2 was curtailed by three weeks as compared with that in cases 3 and 4.

Figure 11 (case 5) corroborates Kanavel's [3] theory with regard to the cause of bone felon. His contention was that the distal phalanx has

3. Kanavel, A. B.: Infections of the Hand, Philadelphia, Lea & Febiger, 1939.

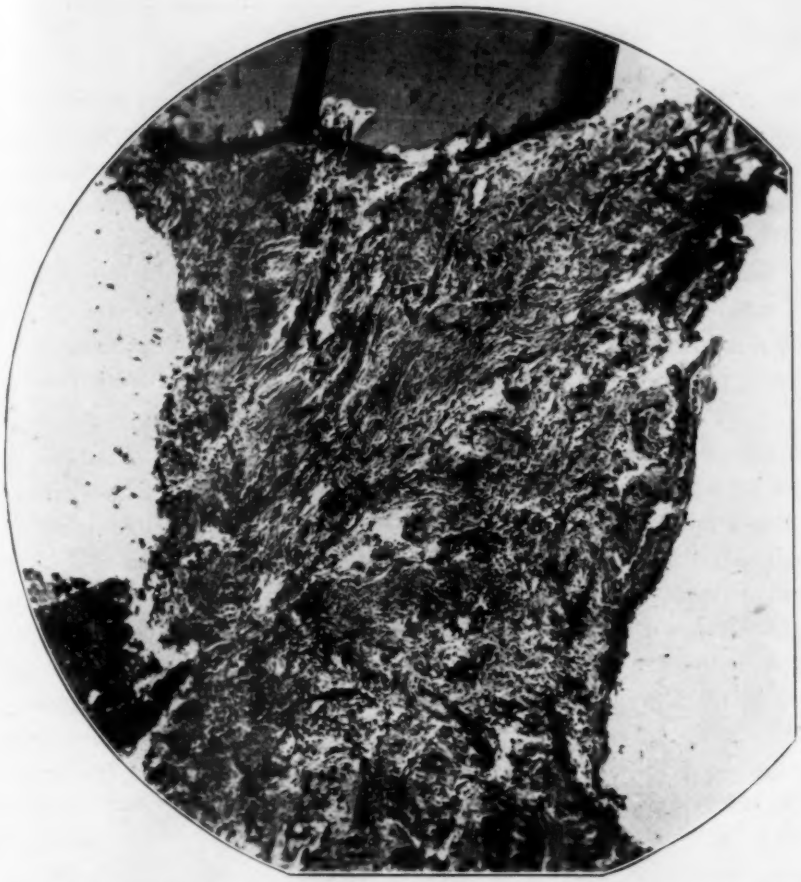

Fig. 4.—Photomicrograph of a section showing production of granulation tissue consisting of new capillaries, fibroblasts, lymphocytic infiltration and deposition of collagen. This is found within the bone marrow.

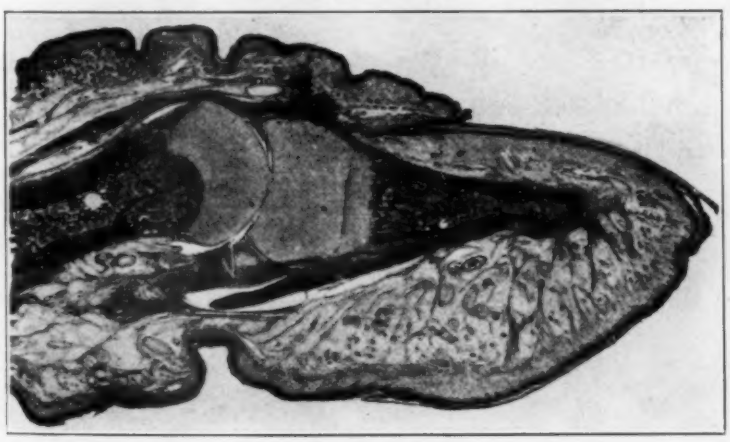

Fig. 5.—Sagittal section of a normal thumb showing the density of the connective tissue trabeculae in the vicinity of the tuft.

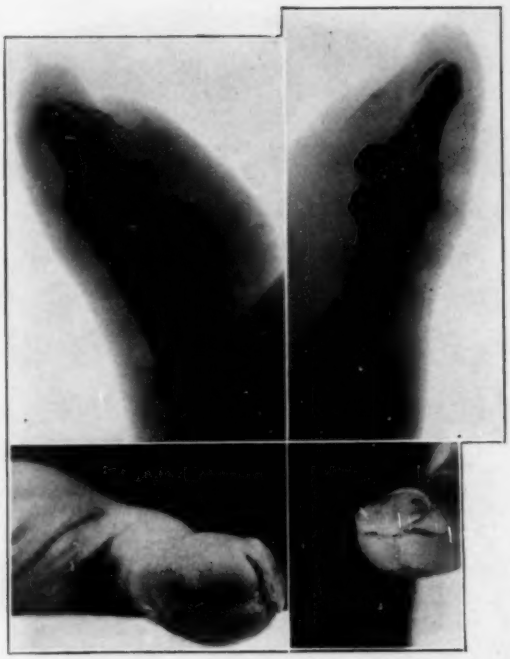

Figure 6

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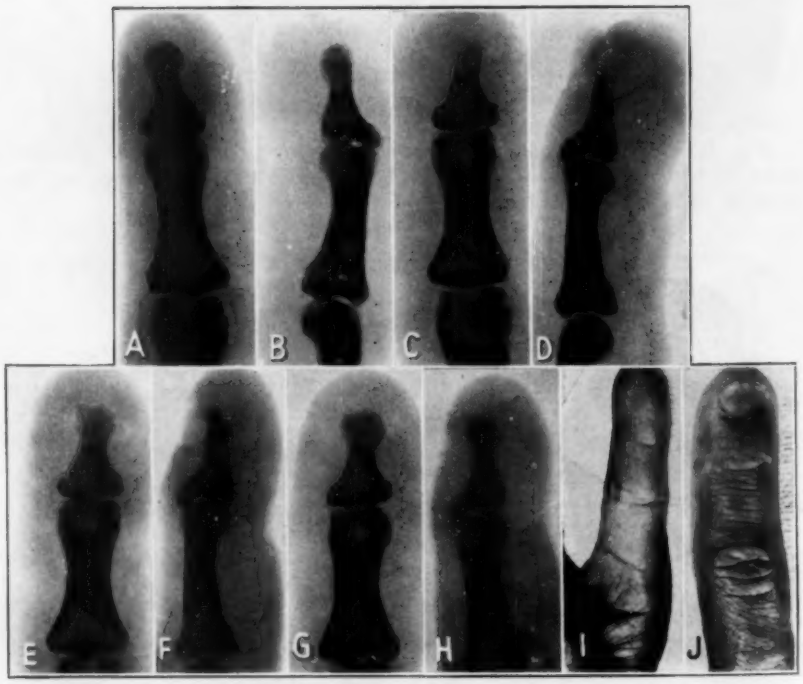

Figure 7

(See legend on opposite page)

a dual blood supply. He stated that owing to edema and pressure on the main blood supply to the diaphysis necrosis of the bone ensues, that the epiphysis lies outside of the closed space and receives a separate blood supply and that early in the disease it is not involved. Even though the major portion of the phalanx is destroyed, if the surgeon retains the base of the phalanx, regeneration invariably ensues. This applies to adults as well as to children. In case 5, a 25 year old white man showed evidence of complete destruction of the distal phalanx. At operation the major portion of the phalanx was removed, and the base was left intact. Within five weeks, the phalanx except for the tuft regenerated.

In case 6 (fig. 12), a white man 25 years of age gave a history of having punctured his right index finger on a piece of metal while he was at work. A few days later the finger swelled and pained him a great deal. The pain was throbbing and kept him awake at night. He went to his family doctor, who made an incision on the volar aspect of the finger extending beyond the distal interphalangeal crease and a lateral incision on the outer aspect of the digit which also crossed the interphalangeal crease. The finger did not drain adequately, and during the third week of his injury the patient presented himself at my office. The finger was swollen, and both incisions were closed by a thick plug of necrotic tissue. Roentgen examination of the index finger revealed evidences of destruction of the distal phalanx and part of the head of the middle phalanx. There were evidences of suppurative tenosynovitis involving the deep flexor tendon. With the patient under general anesthesia, the nail was avulsed, and a horseshoe incision was made around the tuft of the distal phalanx. A large amount of pus and necrotic connective tissue together with the major portion of the phalanx was

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EXPLANATION OF FIGURE 6

Photographs showing the end results of fish mouth incisions in 2 cases.

EXPLANATION OF FIGURE 7

A and *B*, roentgenograms taken in case 1 two days after injury, showing no bone involvement; *C* and *D*, taken after operation at which the tuft of the bone was excised; *E* and *F*, taken one month after operation, showing evidence of regeneration of the phalanx; *G* and *H*, taken six weeks after operation, showing the phalanx completely regenerated. *I* and *J*, photographs showing end results. There is no scar on the volar aspect of the finger, and the new nail has completely regenerated.

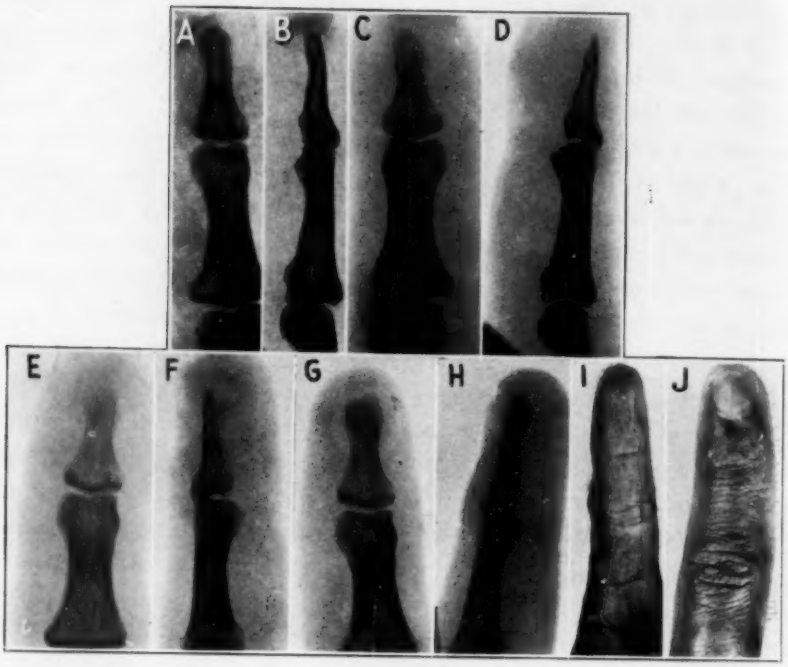

Figure 8
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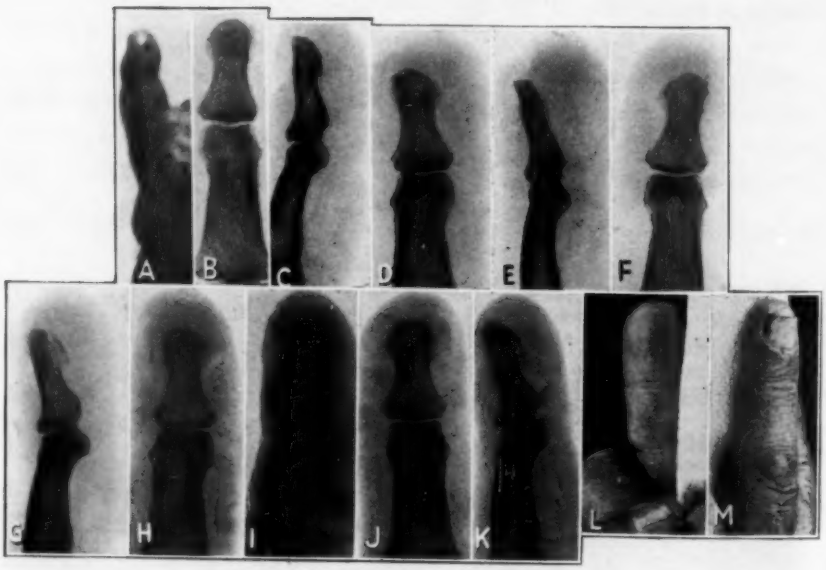

Figure 9
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removed. The wound was packed with iodoform gauze, and a wet dressing was applied. The series of roentgenograms taken during the course of treatment shows that part of the base of the distal phalanx had regenerated and that the flexor profundus tendon remained intact at its insertion into the base of the phalanx. Except for an extension defect in the finger, the functional result was good. The finger was held in a partially flexed position by the contracture of the scar on the volar aspect of the finger.

The end results in cases 1, 2, 3 and 5 showed that scarring on the volar aspect of the finger was absent and that the nail had regenerated. Sensation of the finger was not impaired.

SUMMARY AND CONCLUSIONS

Photomicrographs are presented which show invasion of the bone marrow by infection long before the roentgenogram or the naked eye could perceive evidence of bone destruction.

Comparative studies of cases are presented to show that whenever the tuft of the phalanx is removed early in a case of infection of the anterior space, the healing period is shortened. The tuft is removed only if the connective tissue fibers attached to the bone are edematous or necrotic.

Explanation of Figure 8

A and *B*, roentgenograms taken in case 2 three days after injury, showing no evidence of bone involvement; *C* and *D*, taken after operation at which the perpendicular fibers were found to be necrosed and were removed with the tuft of the bone; *E* and *F*, taken one month after operation, showing that there is no further invasion of bone cells and that regeneration is taking place; *G* and *H*, taken at the end of six weeks, showing the bone completely regenerated. *I* and *J*, photographs showing the end results. There is no scar on the volar aspect of the finger, and the new nail has completely regenerated.

Explanation of Figure 9

A, photograph taken in case 3 seven days after injury, showing the site of the infection. *B* and *C*, anterior and lateral roentgenograms, showing no bone involvement; *D* and *E*, anterior and lateral views taken fourteen days after incision, showing roughening of the phalanx; *F* and *G*, anterior and lateral views taken four weeks later, showing decalcification of the phalanx; *H* and *I*, anterior and lateral views taken eight weeks later, showing decalcification of the phalanx; *J* and *K*, anterior and lateral views taken three months later, showing normal bone; *L* and *M*, photographs showing end results. There is no scar on the volar aspect of the finger, and the new nail has regenerated.

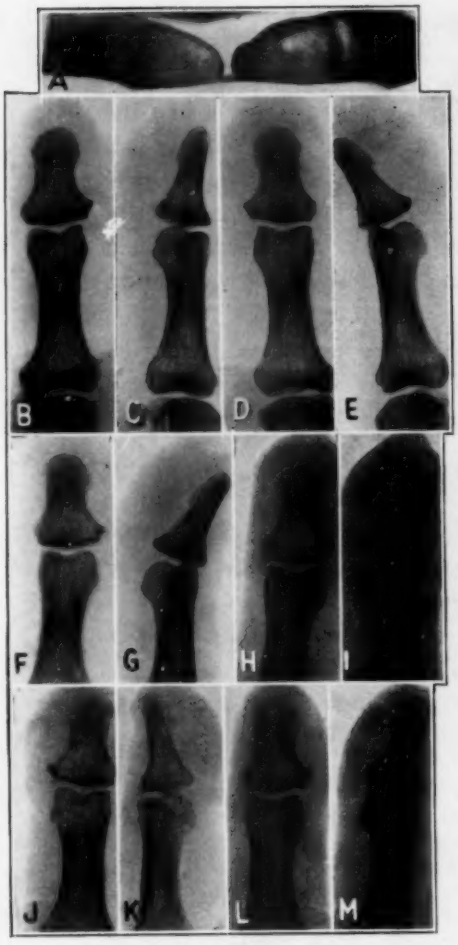

Figure 10

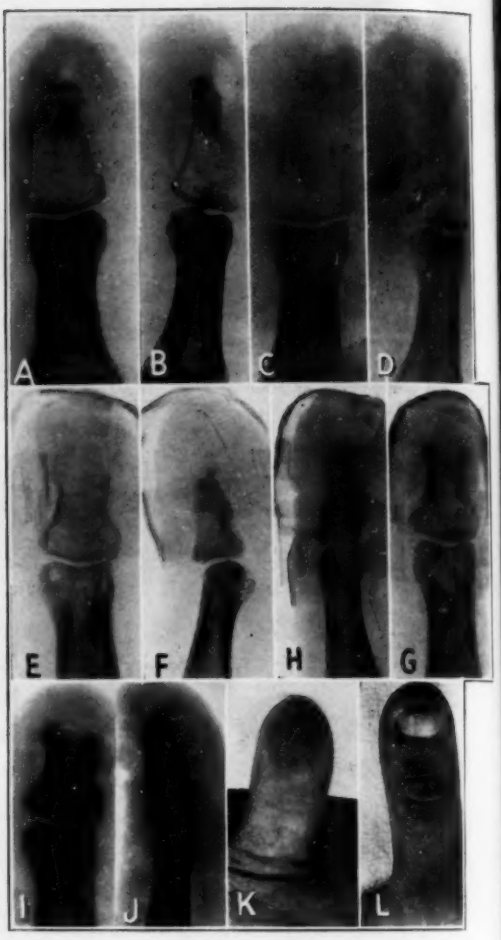

Figure 11

Fig. 10 (case 4).—*A*, comparative photograph showing the normal and the diseased thumb. *B* and *C*, anteroposterior and lateral roentgenograms taken three days after injury, showing no bone involvement; *D* and *E*, taken two weeks, *F* and *G*, four weeks, and *H* and *I*, six weeks, after operation, showing no acute bone involvement; *J* and *K*, taken two months after operation, showing evidences of bone involvement; *L* and *M*, taken three months after operation, showing the phalanx completely regenerated.

Fig. 11 (case 5).—*A* and *B*, roentgenograms taken three weeks after the original injury. The incision was placed on the dorsum of the finger by the family physician. The air pocket indicates the location of the incision. The entire phalanx was destroyed. *C* and *D*, roentgenograms taken immediately after operation, showing a thin shell of base left intact. The patient was 25 years of age. *E* and *F*, roentgenograms taken two weeks after operation, showing regeneration of the phalanx; *G* and *H*, taken one month later; *I* and *J*, taken six weeks after operation, showing the major portion of the distal phalanx regenerated. The tuft is the only part missing. *K* and *L*, photographs taken one year later, showing no scar on the thumb and that the nail is regenerated.

The distal phalanx has a dual blood supply, and removal of the major portion of the phalanx and preservation of the base will often give startling results in the regeneration of the phalanx.

The avulsed nail regenerates in a few weeks and hides the scar. The initial nail may be fissured, but eventually this is replaced by a normal nail. The infection clears, and the wound heals long before the nail regenerates.

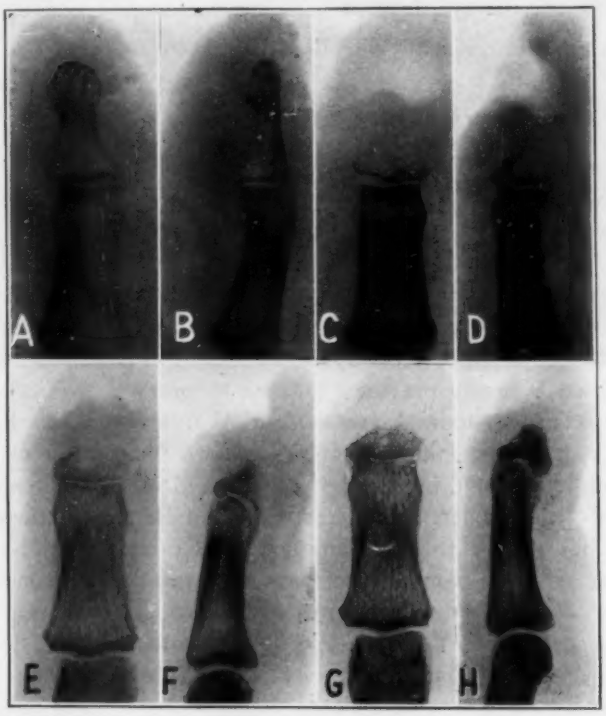

Fig. 12 (case 6).—*A* and *B*, roentgenogram of the index fingers revealing evidences of destruction of the distal phalanx and part of the head of the middle phalanx. There were evidences of suppurative tenosynovitis involving the deep flexor tendon. *C* and *D*, roentgenograms taken immediately after operation; *E* and *F*, taken five weeks after operation; *G* and *H*, taken eight weeks after operation.

Sensation remains intact, and the patient is restored to his or her industry or profession in a short time. Many a needleworker, engraver, pianist, violinist or even surgeon has had to give up his vocation because of impaired sensation or painful scars that have resulted from the fish mouth, hockey stick or median incisions.

REGENERATION OF SERUM ALBUMIN WITH HYDROLYZED PROTEIN IN CHRONIC HYPOPROTEINEMIA PRODUCED BY DIET

AN EXPERIMENTAL STUDY

ROBERT ELMAN, M.D.

LEO A. SACHAR, M.D.

ABRAHAM HORWITZ, M.D.
AND
HARRIET WOLFF, B.A.
ST. LOUIS

Search of the literature reveals no observations on the parenteral use of hydrolyzed protein in the regeneration of serum albumin in animals depleted of their plasma protein by diets deficient in protein. Such a diet has been used by many previous workers to produce hypoproteinemia. The most extensive studies were those of Weech and co-workers.[1] In studies of regeneration, these observers utilized intact proteins, such as meat, serum and casein, but did not employ hydrolyzed protein. Using the Weech diet, Mueller, Kemmerer, Cox and Barnes [2] showed regeneration values similar to those attained with casein when hydrolyzed protein was given by mouth. Increases in serum protein concentration were observed in operative patients with hypoproteinemia after the intravenous injection of the same hydrolyzed protein used in the experiments hereinafter described.[3] The early experimental and clinical observations with hydrolyzed protein were summarized in a previous paper.[4]

This study was aided by grants from the Louis B. Beaumont Fund and Mead Johnson & Co.

From the Department of Surgery, Washington University School of Medicine and Barnes Hospital.

1. (*a*) Weech, A. A.; Goettsch, E., and Reeves, E. B.: J. Exper. Med. **61**:299, 1935. (*b*) Weech, A. A., and Goettsch, E.: Bull. Johns Hopkins Hosp. **63**:154 and 181, 1938; (*c*) **64**:425, 1939.

2. Mueller, A. J.; Kemmerer, K. S.; Cox, W. M., Jr., and Barnes, S. T.: J. Biol. Chem. **134**:573, 1940.

3. Elman, R.: Ann. Surg. **112**:594, 1940.

4. Elman, R., and Weiner, D. O.: Intravenous Alimentation, with Special Reference to Protein (Amino Acid) Metabolism, J. A. M. A. **112**:796 (March 4) 1939.

EXPERIMENTAL PROCEDURE

Thirteen dogs weighing 7 to 12 Kg. were placed on a controlled basal diet (protein and fat free) for five weeks. During the fourth week they were divided into three groups. Group 1 consisting of 4 dogs served as a control and received the basal diet during the entire period of five weeks. Group 2 consisting of 5 dogs received during the fourth week in addition to the basal diet a solution of 5 per cent hydrolyzed protein and 5 per cent dextrose intravenously. The solution was given daily for one week in an amount containing 4 Gm. protein digest (nitrogen, 0.5 Gm.) per kilogram of body weight per day. Group 3 consisting of 4 dogs received the same amount of hydrolyzed protein; this was added to the oral feeding.

TABLE 1.—*Serum Albumin and Nitrogen Balances*

Dog	Weight at Three Weeks (Kg.)	Serum Albumin (Gm. per 100 Cc.) Initial	After Three Weeks	After Four Weeks	After Five Weeks	Change in Albumin During Fourth Week	Nitrogen Balance (Gm. per Week) During Third and Fifth Weeks (Average)	During Fourth Week	Percentage of Nitrogen Supplied by Protein Hydrolysate Utilized
Group 1.—Controls Receiving No Protein Hydrolysate									
1	...	3.68	3.17	2.95	2.89	−0.22	.....	.....	..
2	...	4.18	2.60	2.69	2.48	+0.09	.....	−8.25	..
3	...	4.13	3.05	2.60	2.72	−0.45	.....	−7.12	..
4	...	3.11	2.36	2.32	2.44	−0.04	.....	−5.11	..
Average	...	3.78	2.79	2.64	2.63	−0.15	.....	.....	..
Group 2.—Protein Hydrolysate Given Intravenously During the Fourth Week Only									
5	8.0	3.85	2.51	3.29	3.69	+0.78	−7.3	+7.82	56
6	7.3	3.30	2.03	2.46	2.15	+0.44	−8.7	+5.57	57
7	5.6	3.92	2.61	3.07	2.68	+0.56	−6.0	+5.45	55
8	6.0	3.08	2.35	2.44	2.40	+0.09	−6.2	+5.18	54
9	6.2	3.39	2.01	2.27	2.25	+0.26	−9.1	+2.03	51
Average	6.6	3.51	2.30	2.71	2.63	+0.43	−7.5	+5.21	54.6
Group 3.—Protein Hydrolysate Given by Gavage During the Fourth Week Only									
10	8.0	3.68	2.63	2.79	3.09	+0.16	−5.4	+10.7	61
11	9.8	3.54	2.75	3.12	3.08	+0.37	−7.8	+12.7	64.5
12	9.5	4.25	2.52	2.99	3.08	+0.47	−6.3	+10.6	50.2
13	10.8	4.27	2.57	3.04	2.62	+0.47	−6.2	+12.2	50.8
Average	9.5	3.98	2.62	2.98	2.97	+0.37	−6.4	+11.5	56.6

Basal Diet.—The daily basal intake consisted of 1,000 cc. of 12.5 per cent sucrose and 0.05 per cent vitamin B complex concentrate[5] in Ringer's solution. This solution was given twice daily by gavage. The daily caloric intake per dog was 500 calories. The nitrogen intake while a dog was being given the basal diet (owing almost entirely to the content of the vitamin B complex concentrate) was only 0.07 Gm. per day. Water was allowed ad libitum, but no other fluids or foods were given.

Hydrolyzed Protein.—The hydrolysate[6] used in these experiments was a purified hydrolysate of casein and pork pancreas consisting of amino acids and polypeptides. It was nonantigenic, and its nitrogen content was 12.5 per cent. When

5. The vitamin B complex concentrate (Labco) used in three experiments obtained from the Borden Company, Bainbridge, N. Y.

6. The hydrolyzed protein (Amigen) used in these experiments was furnished by Mead Johnson & Co., Evansville, Ind.

it was given by mouth, the powder was simply added to the gavage feeding given as described.

Parenteral Injection.—Parenteral administration was carried out by continuous injection over a period of six to eight hours into the veins of the extremities. The dogs were unanesthetized and suspended in a canvas frame. When the solution entered at the stated rate, no significant symptoms developed during the venoclysis. Solutions used were prepared by dissolving the hydrolyzed protein and dextrose in hot freshly distilled water to make a solution containing 5 per cent of each. This solution was then passed through a Berkfeld filter into sterile bottles and sterilized by immersion in boiling water for thirty minutes. In dogs receiving this mixture parenterally, the amount of carbohydrate equivalent to that contained in the solution was subtracted from the basal diet so that the carbohydrate intake remained constant.

Studies of Nitrogen Balance.—All dogs were kept in individual metabolism cages. The feces under the conditions of the experiment were scanty and infrequent; the nitrogen content of these was measured in a few cases but found to be constant and so slight that they were not saved for further analysis. During the third, fourth and fifth weeks of the experiment the twenty-four hour urine

TABLE 2.—*Average Serum Globulin Concentration* *

	Dogs	Initial	After One Week	After Three Weeks	After Four Weeks	After Five Weeks
Group 1	5	2.30	2.24	2.32	2.42	2.49
Group 2	4	2.51	2.81	2.69	2.58	2.70
Group 3	4	2.36	2.31	2.59	2.52	2.42
Average	13	2.39	2.48	2.54	2.51	2.55

* Values are given in grams per hundred cubic centimeters.

was collected in receptacles containing thymol as a preservative and sufficient acid to neutralize ammonia. The daily volume of urine was carefully measured and combined for each metabolism period of one week before analysis. In some cases, however, each day's urine was analyzed separately.

Blood Samples.—Blood for chemical analysis was obtained from the external jugular vein, care being taken to obtain a minimum of stasis. Samples were taken at the start of the experiment after one, three, four and five weeks.

Analytic Procedures.—Determinations of total serum proteins and serum albumin were done in duplicate by measuring the nitrogen content of a suspension of the serum in a solution of sodium chloride. The micro-Kjeldahl and titration procedures were those described by Sobel, Yuska and Cohen.[7] Separation of the albumin from the globulin fraction was effected by the method of Campbell and Hanna.[8] Urinary nitrogen was determined by the micro-Kjeldahl procedure.

FINDINGS

On a basal diet consisting entirely of water, electrolytes, sucrose and vitamin B complex concentrate, with practically no nitrogen, dogs exhibited a progressive fall in the albumin fraction of the blood almost

7. Sobel, A.; Yuska, H., and Cohen, J.: J. Biol. Chem. **118**:443, 1937.
8. Campbell, W. R., and Hanna, M. I.: J. Biol. Chem. **119**:15, 1937.

entirely like that of previous observations,[9] in which other types of low or nonprotein diet were used. As in the previous studies there was little significant change in the concentration of globulin (table 2). The total fall during the first three weeks amounted to about 30 per cent of the initial value. During the fourth and fifth weeks the albumin concentration of the control group (1) continued to fall but to a lesser degree.

During the week in which the dogs (group 2) were given the protein hydrolysate intravenously, there was a definite increase in the serum albumin concentration amounting to an average of 0.43 Gm. per hundred cubic centimeters, or 18.7 per cent above the depletion level. The albumin increase in the dogs (group 3) receiving the protein hydrolysate

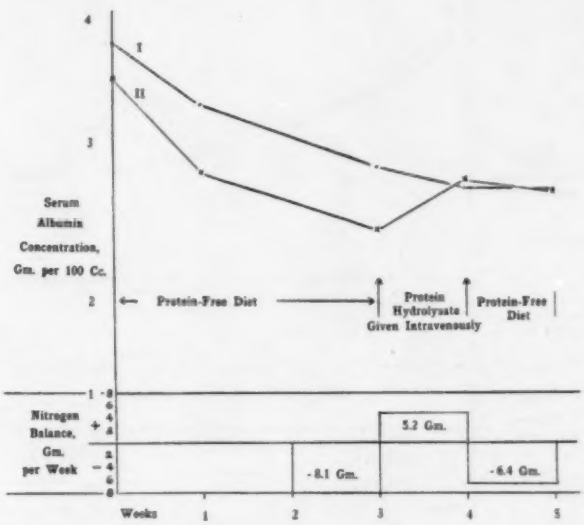

Chart 1.—Average serum albumin changes in dogs given a protein-free diet. I, control dogs, untreated; II, dogs given protein hydrolysate intravenously during the fourth week. Data on nitrogen balance is given for the latter. Note the drop in albumin concentration in both curves and the rise in curve II accompanied by a positive nitrogen balance during the week of treatment with protein hydrolysate.

by mouth was 0.37 per cent, or 14.1 per cent of the depletion value. Thus it is evident that the protein hydrolysate produces about the same rise in the serum albumin whether the material is given intravenously or by mouth.

The studies of nitrogen balance are especially significant and were analyzed to determine the efficiency of the protein hydrolysate, i. e., what

9. Elman, R., and Heifetz, C.: J. Exper. Med. **73**:417, 1941. Weech, Goettsch and Reeves.[1a]

part of the amount given was actually retained. The calculation was made as follows: The nitrogen output of each animal during the third and fifth weeks was averaged and taken as the nitrogen output due to endogenic metabolism. During the fourth week (i. e., when the protein hydrolysate was administered), the nitrogen output was of course much higher. To determine the portion originating from the protein hydrolysate, the endogenic nitrogen value was subtracted from the actual output of nitrogen during this week. This figure represented the amount of nitrogen appearing in the urine supplied by the protein hydrolysate. When this was subtracted from the amount of nitrogen administered, a

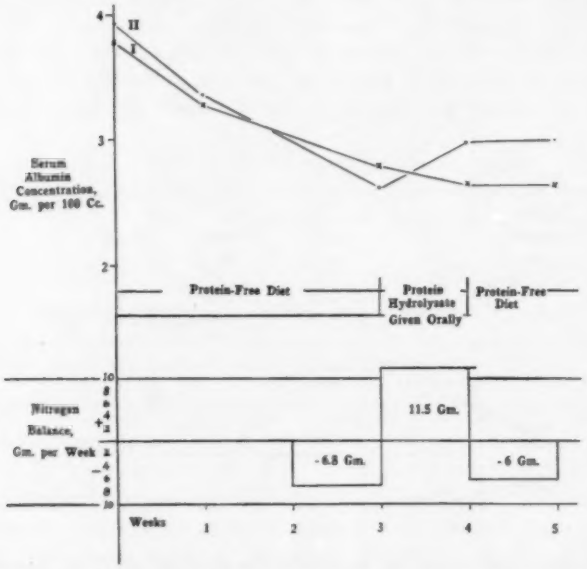

Chart 2.—Average serum albumin changes in dogs given a protein-free diet. I, control dogs, untreated; II, dogs receiving protein hydrolysate by mouth during the fourth week. Data on nitrogen balance is given for the latter. Note the drop in albumin concentration in both curves and the rise in curve II accompanied by a positive nitrogen balance during the week of treatment with protein hydrolysate.

value was obtained representing the amount of nitrogen retained by the dogs. As can be seen from chart 1, an average of 54.6 per cent of nitrogen supplied by the protein hydrolysate was retained in the dogs receiving the hydrolysate parenterally, while 56.6 per cent was retained by those receiving it by mouth. From this it is obvious that there is little significant difference in the percentage of nitrogen retained whether the protein hydrolysate is given by mouth or intravenously.

Another interesting calculation was made on the relation between the increase of the serum albumin and the amount of nitrogen retained during the week of therapy with the protein hydrolysate. By assuming that the plasma volume is one twentieth of the body weight, it is possible to determine the amount of total plasma albumin which was regenerated during the week of treatment. This figure is then compared with the amount of nitrogen retained. For example, dog 6 gained 1.60 Gm. of serum albumin (estimated plasma volume of 365 cc. × .44), or 0.256 Gm. of nitrogen, during the week of therapy. The nitrogen retained during this week was 5.57 Gm. The proportion is 0.256: 5.57, or 2.18

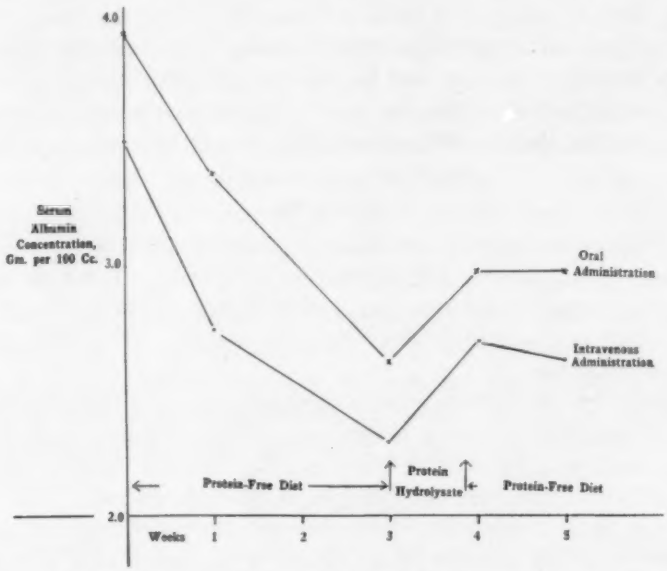

Chart 3.—Comparison of changes in the average serum albumin concentration of dogs receiving protein hydrolysate enterally and parenterally. Note the similarity of the two curves.

per cent. In other words, but a small percentage (the average was 3.5) of the nitrogen retained actually went into the manufacture of serum albumin. To put the matter another way—of the nitrogen retained during the period of treatment with the protein hydrolysate about thirty times as much went to the tissue protein as that which could be accounted for by the increase in the serum albumin.

COMMENT

It seems evident from the data presented in these experiments that the nitrogen in an almost completely hydrolyzed protein leads to about the same degree of regeneration of serum albumin whether given by

mouth or by vein. Moreover, observations of nitrogen balance indicate that the same amount of nitrogen is retained whether the intravenous or the oral route is employed.

The rise in serum albumin averaged about 0.4 Gm. per hundred cubic centimeters during the week of therapy. This is somewhat larger than similar studies already mentioned,[10] in which, however, somewhat smaller doses of protein were given. Nevertheless, it is disappointing from the therapeutic point of view that such a large dose of the protein hydrolysate as 4 Gm. per kilogram per day was needed to achieve this rise. On the other hand, calculations noted before suggest that only a small proportion of the retained nitrogen can actually be utilized for the regeneration of serum albumin; on such a basis it is not surprising that large amounts must be given to effect a significant increase in the concentration of the plasma albumin. It may well be that the difficulties often experienced in correcting severe degrees of nutritional hypoproteinemia have been due to the fact that insufficient amounts of protein were employed.

SUMMARY

In dogs receiving only sucrose and vitamin B concentrate in Ringer's solution, a progressive fall in the concentration of serum albumin develops, averaging 1.2 Gm. per hundred cubic centimeters, or about 30 per cent of the initial value, in three weeks. The serum globulin remains unchanged.

Administration to these protein-depleted dogs of 4 Gm. per kilogram of body weight per day of hydrolyzed protein for one week leads to positive nitrogen balance and appreciable increase (regeneration) of serum albumin (0.4 Gm. per hundred cubic centimeters).

There is no significant difference in the proportion of nitrogen retained or in the amount of serum albumin regenerated whether the hydrolysate is given by mouth or intravenously.

Study of the data on nitrogen balance indicates that 96.5 per cent of the nitrogen retained by animals during the week of therapy with the protein hydrolysate is utilized for the replenishment of the tissue proteins, while only about 3.5 per cent can be accounted for in the replenishment of serum albumin.

10. Weech and Goettsch,[1b] Mueller, Kemmerer, Cox and Barnes.[2]

HYPOPROTEINEMIA IN SURGICAL DISEASES

RELATION OF THE SERUM PROTEIN LEVEL TO HEPATIC FUNCTION AND THE INFLUENCE OF THE TRANSFUSION OF ASCITIC FLUID

HARRY A. DAVIS, M.D.
AND
PAUL L. GETZOFF, M.D.
NEW ORLEANS

The significance of the hypoproteinemic state with regard to operation has been recognized only during the past few years. As a result, a considerable amount of investigation, experimental and clinical, has been carried out on the problems associated with the causation and the therapy of hypoproteinemia. These problems at first appeared to be simple, but with a greater understanding of the syndrome associated with hypoproteinemia came the realization that many questions still remain unanswered. Patients with hypoproteinemia exhibit puzzling variations in their responses to treatment. The problem is not merely one of protein replacement. It is our purpose here to present a classification of the various forms of hypoproteinemia, to examine the causative factors involved in various hypoproteinemic states and to describe the results of the transfusion of ascitic fluid in this group of patients.

CLASSIFICATION

Any classification is useful only so far as it tends to clarify the factual knowledge on which it is based. To be accurate it must rest on a substrate of proved facts. The classification hereinafter presented is based on present day knowledge of the physiology of plasma protein formation. The central site of formation of the plasma proteins is the liver. The evidence in this regard appears to be least equivocal with respect to plasma fibrinogen. This is formed entirely in the liver. If the liver is removed or if it is severely damaged by phosphorus or chloroform, there occurs a marked fall in the plasma fibrinogen. With regard to albumin, the evidence points strongly toward the liver as the only site of formation. Thus, partial hepatectomy or the production of

From the Departments of Surgery and Urology, Louisiana State University School of Medicine, and the Charity Hospital.

an Eck fistula results in a lowering of the plasma albumin level. Plasma globulins, on the other hand, represent a mixture of proteins, the origins of which are probably varied. Undoubtedly, most of them are formed in the liver. But it is likely that certain of them may be produced by many other tissues and that the reticuloendothelial system is an important site of formation. The replacement of the plasma proteins takes place from two sources: (1) exogenic—from ingested food; (2) endogenic—from the reserve store of plasma protein–building material.

In the final analysis, of course, the plasma protein level is dependent on the continued ingestion of material which can be utilized for the formation of plasma proteins. The first evidence brought forward to show that the diet is a potent factor in the regeneration of depleted

TABLE 1.—*Classification of Hypoproteinemia in Relation to Causation*

Type of Hypoproteinemia	Causes of Experimental Hypoproteinemia	Causes of Clinical Hypoproteinemia
1. Prehepatic	Low protein diet; Eck fistula	Malnutrition; anorexia; obstructive lesions of the esophagus or the pylorus; achylia and achlorhydria; gastrectomy; diarrhea; jejunostomy; ileostomy; jejunocolic fistula
2. Hepatic	Partial hepatectomy; chloroform and phosphorus poisoning of the liver; production of abscesses	Hepatitis; acute atrophy of the liver; cirrhosis of the liver; chronic atrophy of the liver (Thompson, McQuarrie and Bell [23a]); chloroform poisoning of the liver; tuberculosis of the liver; infection with or without abscess formation; thyrotoxicosis
3. Posthepatic	Plasmapheresis; hemorrhage; plasma loss by: injections of bile, burns, trauma, freezing and dehydration	Chronic loss of blood; helminthic infection, including hookworm disease; chronic protein loss, e. g., from nephrosis and suppurating wounds; repeated removal of ascitic fluid; acute plasma loss in burns, trauma and various types of peritonitis; chronic bile peritonitis; dehydration

plasma proteins was that of Kerr, Hurwitz and Whipple.[1] The proteins in the food influence not only the regeneration of plasma albumin but also that of plasma globulin.[2] After the amino acids reach the liver by the portal vein from the intestinal tract, they are built partly into proteins and partly into plasma protein–building material. A portion of this synthesized material is placed in the reserve store of plasma proteins. These stores lie mainly in the liver but are present also in

1. Kerr, W. J.; Hurwitz, S. H., and Whipple, G. H.: Regeneration of Blood Serum Protein: II. Influence of Diet upon Curve of Protein Regeneration Following Plasma Depletion, Am. J. Physiol. **47**:370-378 (Dec.) 1918.

2. Holman, R. L.; Mahoney, E. B., and Whipple, G. H.: Blood Plasma and Protein Regeneration Controlled by Diet: I. Liver and Casein as Potent Diet Factors, J. Exper. Med. **59**:251-267 (March) 1934. Pommerenke, W. T.; Slavin, H. B.; Kariher, D. H., and Whipple, G. H.: Blood Plasma Protein Regeneration Controlled by Diet: Systematic Standardization of Food Proteins for Potency in Protein Regeneration, ibid. **61**:261-282 (Feb.) 1935.

many other tissues. In these reserves are placed the precursors of the plasma proteins, although a portion is stored as fully formed protein, which is then available instantly in times of stress. It is apparent, therefore, that the cycle of plasma protein formation revolves around the liver, both from the viewpoint of formation and from that of storage. With these facts in mind, we have classified hypoproteinemia into three types: (1) prehepatic hypoproteinemia; (2) hepatic hypoproteinemia, and (3) posthepatic hypoproteinemia (table 1). Hypoproteinemia of the prehepatic type is caused by interference with adequate intake, digestion or absorption of plasma protein-building materials. In this type the ability of the liver to form plasma proteins is not affected, but the supply of protein–building material is inadequate. There occurs, in other words, a prehepatic deviation of the material necessary for the building of plasma protein. Hypoproteinemia of the hepatic type results from the inability of the liver itself to build the plasma proteins, despite the fact that adequate supplies of plasma protein–building material are received from the intestine. In posthepatic hypoproteinemia there is an adequate formation of proteins by the liver, but an abnormal source of loss of plasma proteins is present. This classification will now be examined in the light of the causation of the hypoproteinemic state as seen in man and in the experimental animal.

CAUSATIVE FACTORS

One must not confuse the causation of hypoproteinemia with the causation of the secondary manifestations of that state, e. g., edema, since it is possible to have one without the other. In the prehepatic type of hypoproteinemia, the causative factors are those producing inadequate intake, deficient digestion or insufficient absorption of plasma protein–building material. Thus there is nutritional edema or famine edema,[3] hypoproteinemia associated with inadequate intake due to a benign or a malignant stricture of the esophagus, reduction of food intake due to indigestion or to pain associated with a gastric ulcer or gastric carcinoma[4] or to vomiting due to pyloric stenosis. Another cause is inadequate digestion of protein due to previous gastrectomy[5] or to achlorhydria associated with diffuse toxic goiter[6] or with pernicious

3. Schittenhelm, A., and Schlecht, H.: Ueber die Oedemkrankheit, Ztschr. f. d. ges. exper. Med. **9**:1-103, 1919.

4. Sisto, P.: La forma idropico-anemica del cancro dello stomaco, Minerva med. **1**:267-273 (March) 1937.

5. Netoušek, M.: Observation d'un cas d'oedème généralisé chez un ancien réséqué d'estomac. Disparition des oedèmes après opothérapie gastrique, Arch. d. mal. de l'app. digestif **25**:984-986 (Nov.) 1935.

6. Mussio-Fournier, J. C.; Castiglioni, C. A., and Anido, J. B.: Oedèmes mous, hypoprotéinémie et anachlorhydrie chez une malade atteinte de goître exophtalmique, Rev. neurol. **1**:756-760 (May) 1934.

anemia.[7] Deficient intake of protein may occur in the aged owing to anorexia and may lead to hypoproteinemia.[8] Endemic forms of edema are also due to low protein diets and have been observed in various parts of the world, e. g., in Annam, part of French Indochina.[9] Inadequate absorption of food may occur as a result of diarrhea and may produce hypoproteinemia, particularly in children.[10] Similarly, defective absorption of food may occur in the presence of jejunostomy, ileostomy or cecal fistula,[11] tuberculosis of the small intestine,[12] regional enteritis[13] and jejunocolic fistula.[14] Pain during defecation as a result of a benign or a malignant stricture of the rectum may cause the patient to reduce the intake of food so that hypoproteinemia develops. The use of poorly balanced diets by patients with diabetes can result in malnutrition and hypoproteinemia. In diabetes mellitus associated with hypoproteinemia, edema will occur only in the absence of acidosis.[15] In the prehepatic type of hypoproteinemia, does a deficient intake of protein provide an adequate explanation of the causation? The contention of Bloomfield[16] that additional unknown factors also are involved has been supported by later investigators.[17] However, it should be pointed out that some con-

7. Meulengracht, E.; Iversen, P., and Nakazawa, F.: Edema and Water Excretion in Pernicious Anemia, Ugesk. f. læger **89**:1020-1023 (Nov. 10) 1927.

8. Durand, P.: Les oedèmes par carence alimentaire chez les vieillards, Rev. gén. de clin. et de thérap. **49**:855-856 (Dec.) 1935.

9. Normet, L.: Renseignements complémentaires sur la pathogénie de la bouffissure d'Annam, maladie de carence, Bull. Acad. de méd., Paris **117**:239-242 (Feb.) 1937.

10. Ariztia, A.: Sindromas edematosos con hipoproteinemia en el niño menor, Rev. chilena de pediat. **9**:1-13 (Jan.) 1938. Schwarzenberg, L. J., and Cousino, J.: Dos casos de edemas generalizados con hipoproteinemia, ibid. **9**:747-755 (Sept.) 1938.

11. Wolferth, C. C.: Inanition Edema Associated with Alimentary Disturbances in Adults, M. Clin. North America **8**:785-801 (Nov.) 1924.

12. Landis, E. M., and Leopold, S. S.: Inanition Edema Associated with Tuberculous Enteritis, J. A. M. A. **94**:1378-1381 (May 3) 1930.

13. Casten, D.: Nutritional Disturbances in Regional Enteritis, Surgery **6**:703-716 (Nov.) 1939.

14. deNavasquez, S.: Nutritional Edema as a Complication of Jejunocolic Fistula, Brit. J. Surg. **28**:468-471 (Jan.) 1941.

15. Peters, J. P.; Bulger, H. A., and Eisenman, A. J.: The Plasma Proteins in Relation to Blood Hydration: II. In Diabetes Mellitus, J. Clin. Investigation **1**:451-472 (June) 1925.

16. Bloomfield, A. L.: The Effect of Restriction of Protein Intake on the Serum Protein Concentration of the Rat, J. Exper. Med. **57**:705-720 (May) 1933.

17. (*a*) Weech, A. A.; Goettsch, E., and Reeves, E. B.: Nutritional Edema in the Dog: I. Development of Hypoproteinemia on a Diet Deficient in Protein, J. Exper. Med. **61**:299-317 (March) 1935. (*b*) Youmans, J. B.; Bell, A.; Donley, D., and Frank, H.: Endemic Nutritional Edema: II. Serum Proteins and Nitrogen Balance, Arch. Int. Med. **51**:45-61 (Jan.) 1933.

fusion has arisen here between the causation of hypoproteinemia and the causation of the secondary manifestations, such as edema. Hypoproteinemia of the prehepatic type seems to be definitely related to an inadequate supply of plasma protein–building materials to the liver, since the provision of a high protein diet causes the disappearance of hypoproteinemia. However, other factors besides hypoproteinemia are probably involved in the causation of edema since this does not always disappear simultaneously with a rise in the serum protein level.[17b]

As has been stated previously, hepatic hypoproteinemia results from the inability of the liver to synthesize plasma proteins despite an adequate supply of precursor material. Intrinsic disease of the liver may be associated with edema.[18] More recently, hypoproteinemia and edema have been noted in association with extreme tuberculous involvement of the liver,[19] with subacute yellow atrophy of the liver,[20] with syphilis of the liver,[21] with portal cirrhosis of the liver [22] and with idiopathic liver atrophy.[23] The association of hypoproteinemia and edema with intrinsic disease of the liver appears to be well established. Nevertheless, edema without hypoproteinemia has been observed in acute yellow atrophy of the liver [24] and in catarrhal jaundice.[25]

Extrahepatic infections may result in hypoproteinemia. It has been shown that the production of an abscess will inhibit protein regeneration by the liver.[26] Another important factor is the loss of protein into the

18. Schrumpf, A.: Ein Fall von Leberinsuffizienz mit Ödemen, Klin. Wchnschr. **9**:2444 (Dec. 27) 1930.

19. May, E., and Braillon, J.: Grande anasarque primitive: Hépatite hypertrophique graisseuse tuberculeuse sans lésions rénales, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1597-1602 (Dec. 10) 1934.

20. Caroli, J.; Cachera, R., and Deparis, M.: Les formes hydropiques de l'ictère catarrhal, Paris méd. **1**:435-439 (May 16) 1936.

21. Weech, A. A.: Nutritional Edema, Internat. Clin. **2**:223-248 (June) 1936.

22. Baumel, J., and Serre, H.: Le syndrome hydropigène dans les maladies du foie, Rev. méd.-chir. d. mal. du foie **12**:65-121 (March-April) 1937. Eisenfarb, J.: Anémie hyperchrome au cours d'un ictère grave. Contribution à l'étude de l'anémie hyperchrome et de l'oedème au cours des affections parenchymateuses aiguës du foie, ibid. **13**:271-281 (July-Aug.) 1938.

23. (*a*) Thompson, W. H.; McQuarrie, I., and Bell, E. T.: Edema Associated with Hypogenesis of Serum Proteins and Atrophic Changes in the Liver, J. Pediat. **9**:604-619 (Nov.) 1936. (*b*) Myers, W. K., and Taylor, F. H. L.: Hypoproteinemia Probably Due to Deficient Formation of Plasma Proteins, J. A. M. A. **101**:198-200 (July 15) 1933.

24. Loeper, M.; Roy, A.; Perreau, P., and Varay, M.: L'oedème des hépatites ictérigènes graves, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1173-1180 (July 13) 1936.

25. Cernich, R.; Palazón, J. M., and de Lellis, J. D. M.: Hepatitis icterígena con edema, Semana méd. **2**:1008-1010 (Oct. 8) 1936.

26. Madden, S. C.; Winslow, P. M.; Howland, J. W., and Whipple, G. H.: Blood Plasma Protein Regeneration as Influenced by Infection, Digestive Disturbances, Thyroid and Food Proteins, J. Exper. Med. **65**:431-454 (March) 1937.

site of suppuration. The diminution of liver function so frequently associated with thyrotoxicosis may explain in part the occurrence of hypoproteinemia and edema in a patient suffering from toxic diffuse goiter.[6]

The posthepatic type of hypoproteinemia results from a loss of fully formed plasma protein from the body. This may be produced experimentally by plasmapheresis, hemorrhage, subcutaneous or intraperitoneal injections of bile,[27] burns, trauma and freezing. Clinically, a variety of conditions may lead to protein loss. Protracted loss of blood is an occasional factor. Hypoproteinemia and edema have been noted in association with the helminthic types of anemia, particularly ankylostomiasis and intestinal bilharziasis.[28] Loss of plasma protein into localized areas as a result of burns or trauma will cause hypoproteinemia which may be unrecognized until fluids are administered and edema occurs. Infections associated with suppuration are an important cause of hypoproteinemia of the posthepatic type. The amount of protein which is lost in pus is considerable and has been estimated to vary from 8.1 to 21 Gm. per hundred cubic centimeters of total protein and from 4.6 to 11.5 Gm. per hundred cubic centimeters of albumin.[29] This would explain in part the occurrence of hypoproteinemia and edema in appendical abscess,[30] peritonitis,[31] infected burns,[32] empyema[29b] and suppurating lung cysts.[33] Diarrhea, if associated with loss of blood and pus, may lead to hypoproteinemia and edema, e. g., in chronic ulcerative colitis[34] and in dysentery.[35] In severe dehydration, a breaking

27. Harkins, H. N.; Harmon, P. H., and Hudson, J. E.: Lethal Factors in Bile Peritonitis: I. "Surgical Shock," Arch. Surg. **33**:576-608 (Oct.) 1936.

28. Salah, M.: Mechanism of Oedema in Helminthic Anemias, Tr. Roy. Soc. Trop. Med. & Hyg. **31**:431-436 (Jan.) 1938.

29. (*a*) Jones, C. M.; Eaton, F. B., and White, J. C.: Experimental Postoperative Edema, Arch. Int. Med. **53**:649-674 (May) 1934. (*b*) Mauriac, P.: Oedème et suppuration pleurale tuberculeuse, Presse méd. **44**:1215-1216 (July 25) 1936.

30. Meyer, O. O.: Generalized Edema After Surgery, with Case Report, Wisconsin M. J. **33**:427-431 (June) 1934.

31. Curphey, W. C., and Orr, T. G.: Edema in Surgical Patients, Surgery **1**: 589-594 (April) 1937. Jones, Eaton and White.[29a]

32. Clavelin, M., and Hugonot, M.: Oedème généralisé chez un brûlé: Contribution à la pathogénie des oedèmes, Bull. et mém. Soc. méd. d hôp. de Paris **52**:1444-1449 (Nov. 16) 1936.

33. Troisier, J.; Bariety, M., and Hautefeuille, E.: Double kyste pulmonaire suppuré. Cachexie oedémateuse curable, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:417-426 (March 21) 1938.

34. Bargen, J. A., and Brown, P. W.: A Complication of Chronic Ulcerative Colitis Hitherto Not Described, M. Clin. North America **18**:529-533 (Sept.) 1934.

35. Iskander, F.: Post-Dysenteric Edema in Children, J. Egyptian M. A. **18**:134-137 (Feb.) 1935.

down of the plasma proteins occurs with a resultant hypoproteinemia.[36] It should be remembered that all infections, particularly those associated with suppuration, may interfere with protein regeneration by the liver and may thus accentuate hypoproteinemia, if present.

PHYSIOLOGIC EFFECTS OF HYPOPROTEINEMIA

The physiologic effects of hypoproteinemia are readily understood when consideration is given to the functions of the serum proteins. If the discussion is limited to albumin and globulin, the proteins may be said to serve three main functions: (1) maintenance of the osmotic pressure of the blood; (2) maintenance of the hydrogen ion concentration of the blood at normal levels; (3) provision of food material in times of stress. The maintenance of the osmotic pressure of the blood is of great importance in the distribution of fluid between the blood stream and the interstitial tissue spaces. The osmotic pressure of the normal serum is between 21 and 29 mm. of mercury. The osmotic pressure of 1 Gm. of albumin is 5.5 mm. of mercury and of 1 Gm. of globulin, 1.4 mm. of mercury. As the concentration of the serum proteins is increased, each gram exerts more osmotic pressure than it did in more dilute solutions.[37] According to the Starling hypothesis, the distribution of fluids between the blood stream and the extravascular spaces is dependent on the interaction of the hydrostatic pressure of the blood and the osmotic pressure of the serum proteins. From this standpoint, albumin is most effective. Since, however, the rate of regeneration of albumin is slower than that of globulin or fibrinogen, it is found that albumin values tend to be low in hypoproteinemia, while those of globulin are reduced, normal or even elevated. This dissociated type of hypoproteinemia, i. e., a lowered albumin level with an elevated globulin level, is most often found in suppurative conditions of long standing.

The effects produced by a reduction of the protein content of the serum will be dependent on the extent and the rate of reduction. The influence of the extent of reduction of proteins is exemplified by the appearance of edema at the critical level, which, according to Moore and Van Slyke,[38] is 5.5 ± 0.3 Gm. per hundred cubic centimeters for total serum proteins and 2.5 ± 0.2 Gm. per hundred cubic centimeters

36. Maes, U., and Davis, H. A.: Fluid Replacement in Surgical States with Particular Reference to Transfusion of Ascitic Fluid: A Clinical and Experimental Study, Arch. Surg. **42**:453-479 (March) 1941.

37. Fishberg, E. H.: The Relations of the Serum Proteins and Lipids to the Osmotic Pressure, J. Biol. Chem. **81**:205-214, 1929. Verney, E. B.: The Osmotic Pressure of the Proteins of Human Serum and Plasma, J. Physiol. **61**:319-328 (June) 1926.

38. Moore, N. S., and Van Slyke, D. D.: The Relationships Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, J. Clin. Investigation **8**:337-355 (April) 1930.

for serum albumin. At this level, the osmotic pressure of the blood is so reduced that the hydrostatic pressure of the blood exceeds it and water passes into the extravascular tissue spaces. The influence of the rate of reduction of the serum proteins is illustrated by the fact that their rapid removal by plasmapheresis may produce "hypoproteinemic" shock.[39] This is due to a reduction of plasma volume and thereby of the blood volume. Clinical analogies to the hypoproteinemic shock of animals are seen in conditions of plasma loss associated with trauma, burns and peritonitis.

TABLE 2.—*Electrocardiographic Studies of Hypoproteinemia*

Patient and Sex	Race and Age, Yr.	Diagnosis	Serum Proteins, Gm. per 100 Cc.	Electrocardiogram
W. B. ♂	W 14	Chronic osteomyelitis; acute glomerulonephritis	3.65	No change
A. B. ♀	W 65	Carcinoma of the rectum	5.0	Slight axis deviation; slight depression of ST segment in leads I and II; R-2 notched on downstroke near base; electrocardiogram suggested overwork of the left ventricle but no evidence of organic disease
E. E. ♀	N 21	Syphilitic cirrhosis of the liver	5.2	No change
J. D. ♂	W 55	Calculous pyonephrosis	6.3	Definite electrocardiographic evidence of myocardiac disease, suggestive of old posterior infarct
L. N. ♀	N 60	Carcinoma of the stomach	3.72	Left axis deviation; all complexes reduced in amplitude; definite electrocardiographic evidence of myocardiac disease
J. C. ♂	N 49	Amebic colitis	5.7	Left axis deviation; P waves wide and notched; low T waves in leads I and II; definite electrocardiographic evidence of myocardiac disease
R. J. ♀	N 27	Toxemia of pregnancy	4.63	Low T waves; ST segments in leads I, II and IV depressed; electrocardiogram suggested toxic condition

Frequently, secondary anemia accompanies hypoproteinemia, but probably the same causative factors underlie both conditions. There are no data available as to the direct effects of hypoproteinemia on hematopoiesis, but it is possible that defective blood formation may result from an insufficient supply of protein-building material. Hypoproteinemia is associated with a reduced blood volume. Hypoproteinemia does not appear to affect cardiac function, since the electrocardiogram exhibits no characteristic changes (table 2). The blood pressure may be normal, elevated or lowered. Not infrequently it is lowered, and this may be

39. Whipple, G. H.; Smith, H. P., and Belt, A. E.: Shock as a Manifestation of Tissue Injury Following Rapid Plasma Protein Depletion: The Stabilizing Value of Plasma Proteins, Am. J. Physiol. **52**:72-100 (May) 1920.

due to reduction of the blood volume. Hypoproteinemia affects the motor activity of the gastrointestinal tract, probably by permitting the occurrence of edema of the wall of the stomach and the intestines. Diminution in peristalsis of the stomach and delay in its emptying time have been noted.[40] This diminution of gastric peristalsis is difficult to reconcile with the finding of intestinal hyperperistalsis and diarrhea in hypoproteinemic dogs.[29a] Clinically, one of us (H. A. D.) has noted diminished intestinal peristalsis in patients with hypoproteinemia such that adynamic ileus was simulated. This was relieved by blood transfusion. The relation of hypoproteinemia to liver function is of great interest. It will be noted that in our patients (table 3 and chart 1) hypoproteinemia was accompanied by a diminution in hepatic function.

The resistance of the liver to various forms of chemical injury and its ability to regenerate after injury are dependent on an adequate intake of protein-building material. In hypoproteinemia, not only is the liver more susceptible to injury, since its functional ability is reduced, but it is less able to regenerate after such injury because of the lowering of the reserves of protein precursors and formed protein.

It is of interest to compare the results of various types of liver function tests in hypoproteinemia. In dogs with hypoproteinemia, Elman and Heifetz [41] found that the excretion of phentetiothalein sodium was diminished. The galactose tolerance test, however, revealed that the liver functioned normally in this respect. DeNavasquez [14] noted that the dextrose and levulose tolerance tests for liver function revealed normal values in his patient with hypoproteinemia. The bromsulfalein test for liver function showed normal values in the patient with hypoproteinemia reported by Mussio-Fournier and co-workers.[6] In our series of patients with hypoproteinemia (table 3), all, without exception, had marked reduction of liver function (intravenous hippuric acid test). These findings suggested that certain tests, e. g., the hippuric acid test, may be more sensitive indicators of the state of liver function than are other tests, e. g., galactose or dextrose tolerance tests, when used in patients with hypoproteinemia.

Extrahepatic infections appear to exert a reversible effect on the function of the liver. This is illustrated in chart 1. As the infection subsides, the return of liver function to normal occurs rapidly. There appears to be a "lag" period between these events (chart 1). There is a coincident rise in the level of the serum proteins. The relative rapidity

40. Mecray, P. M.; Borden, R. P., and Ravdin, I. S.: Nutritional Edema: Its Effect on the Gastric Emptying Time Before and After Gastric Operations, Surgery **1**:53-64 (Jan.) 1937.

41. Elman, R., and Heifetz, C. J.: Experimental Hypoalbuminemia: Its Effect on the Morphology, Function, and Protein and Water Content of the Liver, J. Exper. Med. **73**:417-430 (March) 1941.

TABLE 3.—*Relation of Serum Protein Level to Liver Function*

Patient	Sex	Race	Age, Yr.	Clinical Condition	Total Serum Proteins, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Globulin, Gm. per 100 Cc.	Albumin-Globulin Ratio	Liver Function, Intravenous Hippuric Acid Test, Gm. per 100 Cc.	Edema	Type of Hypoproteinemia	Sources of Protein Defect
W. B.	M	W	14	Chronic osteomyelitis; acute glomerulonephritis	3.65	1.36	2.29	0.59:1	0.27	Pedal, grade 1	Hepatic and posthepatic	Diminished protein regeneration by the liver; loss of protein in urine and pus
R. J.	F	N	21	Toxemia of pregnancy	4.63	1.65	2.98	0.55:1	0.38	Lower extremities and face, grade 4	Hepatic and posthepatic	Diminished protein regeneration by the liver; loss of protein in urine
H. B.	M	W	30	Chronic ulcerative colitis	5.61	2.48	3.13	0.79:1	0.23	Lower extremities, grade 2	Combined*	Insufficient protein intake; loss of protein in feces; diminished protein regeneration by the liver
W. S.	M	W	25	Banti's disease with cirrhosis of the liver	5.5	2.6	2.9	0.89:1	0.27	Dependent portions of the body	Hepatic and posthepatic	Diminished protein regeneration by the liver; loss of protein in ascitic fluid
A. B.	F	W	65	Ulcerative proctitis	5.0	2.23	2.77	0.80:1	0.26	Lower extremities, grade 2	Combined*	Insufficient protein intake; diminished protein regeneration by the liver; loss of blood per rectum
L. N.	F	N	60	Carcinoma of the stomach with obstruction	3.72	1.24	2.48	0.5:1	0.40	Generalized anasarca, grade 3	Prehepatic and hepatic	Insufficient protein intake; diminished protein regeneration by the liver
E. E.	F	N	21	Syphilitic cirrhosis of the liver	5.2	2.0	3.2	0.62:1	0.42	Generalized anasarca, grade 4	Hepatic	Diminished protein regeneration by the liver
J. D.	M	W	55	Calculous pyonephrosis	6.3	1.65	4.65	0.35:1	0.27	Pedal, grade 1	Hepatic and posthepatic	Loss of protein in the urine; diminished protein regeneration by the liver

J. C.	M	N	49	Amebic colitis	5.7	2.25	3.45	0.65 :1	0.37	Pedal, grade 1	Combined*	Insufficient protein intake and absorption; loss of protein in feces; diminished protein regeneration by the liver
J. P.	F	N	38	Pelvic abscess	5.21	.....	.....	.....	0.27	Lower extremities, grade 2	Hepatic and posthepatic	Loss of protein in pus from abscess; diminished protein regeneration by the liver
J. T.	F	N	24	Rectal stricture; anorexia	3.17	.....	.....	.....	0.20	Lower extremities, grade 4	Combined*	Insufficient protein intake and absorption; diminished protein regeneration by the liver; loss of protein in feces
M. L.	F	W	44	Pyonephrosis	5.10	.....	.....	.....	0.396	Lower extremities, grade 2	Hepatic and posthepatic	Loss of protein in urine; diminished protein regeneration by the liver
E. W.	F	N	40	Tuberculous peritonitis; jejunostomy	4.99	.....	.....	.....	0.343	Pedal, grade 4	Combined*	Insufficient absorption of protein; loss of protein in peritoneal exudate; diminished protein regeneration by the liver
E. S.	M	W	56	Cystitis and pyelonephritis	5.02	.....	.....	.....	0.425	Lower extremities, grade 2	Hepatic and posthepatic	Loss of protein in urine; diminished protein regeneration by the liver
D. A.	M	W	61	Prostatic hypertrophy with urinary retention and infection	4.93	.....	.....	.....	0.282	Lower extremities, grade 2	Hepatic and posthepatic	Loss of protein in urine; diminished protein regeneration by the liver
E. V.	M	N	59	Carcinoma of the rectum; infection of the abdominal wall	5.8	.....	.....	.....	0.54	Pedal, grade 3	Combined*	Diminished intake of protein; loss of protein in pus; diminished protein regeneration by the liver
M. W.	M	N	27	Amebic colitis inanition	4.67	2.4	2.27	1.05 :1	0.30	Generalized, grade 4	Combined*	Deficient intake and absorption of protein; loss of protein in feces; diminished protein regeneration by the liver

* Combination of prehepatic, hepatic and posthepatic types.

with which these processes occur suggests that at least in this type of hypoproteinemia there is little depletion of the protein reserves and that the effect of the infection is to render the liver less able to utilize adequately the stores of protein precursor material for protein formation. The duration of the hypoproteinemic state is significant since it has been shown that in dogs prolonged hypoproteinemia further diminishes the ability of the liver to form proteins.[42]

It is difficult to reconcile these facts with the observations of other workers, who have found that patients with hepatic disease, e. g., portal cirrhosis and obstructive jaundice, may exhibit normal plasma protein levels.[42]

The effect of hypoproteinemia on renal function is of interest. Due to prerenal deviation of water into the extravascular tissue spaces, a fall

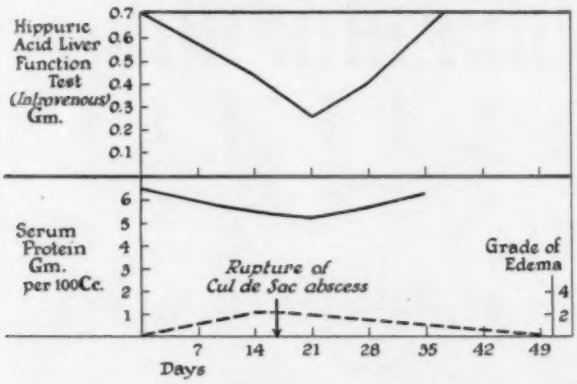

Chart 1.—Relation of serum protein level to hepatic function (patient J. P.).

in the amount of urine secretion occurs. There is, however, no true renal insufficiency. Occasionally, polyuria occurs in the presence of hypoproteinemia and edema. In animals, nephrosis with albuminuria, due to increased permeability of the glomerular capillaries, may follow a prolonged state of hypoproteinemia as a result of repeated plasmapheresis.[43]

INFLUENCE OF HYPOPROTEINEMIA ON THE HEALING OF WOUNDS

The influence of hypoproteinemia on the healing of wounds is well known and therefore will be discussed only briefly here. Clinically, it may be observed that certain patients show difficulty in the healing of

42. Peters, J. P.; Eisenman, A. J., and Bulger, H. A.: The Plasma Proteins in Relation to Blood Hydration: I. In Normal Individuals and in Miscellaneous Conditions, J. Clin. Investigation **1**:435-450 (June) 1925.

43. Leiter, L.: Nephrosis, Medicine **10**:135-242 (May) 1931.

their operative wounds. The rate and the degree of growth of fibroblasts in wounds are increased by a high protein diet.[44] In patients with hypoproteinemia, wound healing is slow, and the tensile strength of the wound is low. The tendency to wound disruption is greater in this group of patients than it is in patients without hypoproteinemia.[45] The influence of hypoproteinemia seems to be limited to proliferation of the fibroblasts.

The growth of epithelium does not appear to be directly affected by hypoproteinemia. When accessory factors, such as wound infection, seroma and foreign bodies, are coexistent, the deleterious effect of hypoproteinemia on the healing of the wound is accentuated.

PATHOLOGIC EFFECTS OF HYPOPROTEINEMIA

The most obvious alterations of tissue structure are those resulting from the disturbance in water distribution, namely, edema. Thus, edema of the subcutaneous tissues and of various viscera, e. g., the lungs, the cardiac muscle, the gastrointestinal tract, the liver, the pancreas, the brain and the skeletal muscle may occur. Collections of fluid may be found in the peritoneal, the pleural, and the pericardial cavity.

Subcutaneous edema is usually first noted in the lower extremities. This is probably due to erect posture which favors the passage of fluid from the capillaries into the interstitial tissue spaces.[46] There does not appear to be a definite correlation between the presence of subcutaneous edema and edema of the viscera, since one may be absent while the other is present, owing to the fact that, while hypoproteinemia is the fundamental underlying cause, other factors are important in determining the time of onset and the distribution of edema. These factors are: (1) the amount of fluid intake; (2) the amount of basic ions, particularly sodium ions, dissolved in the body fluids (an increase in the amount of such ions tends to promote edema[47]); (3) the presence of increased permeability of the capillaries (this may occur as a result of local capillary injury, e. g., from burns or trauma, or as a result of

44. Harvey, S. C., and Howes, E. L.: Effect of High Protein Diet on the Velocity of Growth of Fibroblasts in the Healing Wound, Ann. Surg. **91**:641-650 (May) 1930.

45. Thompson, W. D.; Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption, Arch. Surg. **36**:500-508 (March) 1938.

46. Youmans, J. B.; Wells, H. S.; Donley, D.; Miller, D. G., and Frank, H.: The Effect of Posture (Standing) on the Serum Protein Concentration and Colloid Osmotic Pressure of Blood from the Foot in Relation to the Formation of Edema, J. Clin. Investigation **13**:447-459 (May) 1934.

47. Fahr, G.; Kerkhof, A., and Giere, E.: Salt as a Factor in Edema Formation Following Plasmaphoresis, Proc. Soc. Exper. Biol. & Med. **29**:335-336 (Dec.) 1931. Liu, S. H.; Chu, H. I.; Li, R. C., and Fan, C.: Nutritional Edema: II. Effect of Alkali and Acids on Nitrogen Balance, Plasma Proteins and Edema, ibid. **29**:252-253 (Dec.) 1931.

general capillary injury, e. g., from infection); (4) diminution of tissue pressure (a normal degree of tissue tension or pressure is an important factor in limiting the outflow of fluid from the blood vessels, e. g., those of the lower extremities in the erect posture[46]; a loss of tissue proteins as a result of malnutrition will lower the effective tissue pressure).

The tendency to edema formation seems to vary in different tissues. Thus, in conditions producing acute hypoproteinemia with little tissue protein deficit, there is a greater tendency toward the formation of ascites, hydrothorax and hydropericardium than toward edema of the subcutaneous tissues. Conversely, conditions which produce a depletion of both plasma and tissue protein, as in nutritional deficiency states, will show a higher incidence of subcutaneous edema. The walls of the gastrointestinal tract and the lungs appear to be more frequent sites of edema than do the other viscera. It is significant that these viscera normally have a looser tissue structure than do the liver, the kidneys, the brain or the heart.

Lesions of the tissues other than those associated with edema have been described. It must be remembered, however, that coexistent infection or tissue protein defect may be responsible for the lesions. According to Bablet and Normet,[48] in cases of the endemic form of nutritional edema occurring in Annam, examination of the heart at necropsy revealed partial disappearance of the cardiac muscle fibers and deformations of the muscle nuclei. It is probable that this was more the result of associated tissue protein defect than of hypoproteinemia. The same authors described the presence of fatty metamorphosis of the liver, affecting mainly the middle and central zones of the liver lobules with areas of necrosis in the midzonal areas. Fatty metamorphosis of the liver and brown atrophy of the heart have been described in hypoproteinemia.[14] In a study of the causative factors concerned in the production of postoperative edema, moderate grades of liver necrosis were noted in animals (cats) in which abscesses had been produced.[29a] More conclusive evidence of the effect of hypoproteinemia on the liver was presented by Elman and Heifetz,[41] whose animals when maintained in the hypoproteinemic state for long periods revealed a loss of hepatic cell substance, an increased content of water in the liver and a diminution of liver function.

CLINICAL PICTURE OF HYPOPROTEINEMIA

The picture presented by these patients is subject to puzzling variations. Usually, such patients may be classified in one of three groups:

48. Bablet, J., and Normet, L.: Les lésions histopathologiques de la bouffissure d'Annam, Bull. Acad. de méd., Paris **117**:242-244 (Feb. 23) 1937.

(1) those with cryptic hypoproteinemia; (2) those with hypoproteinemia without edema; (3) those with hypoproteinemia with edema.

In the first group, hypoproteinemia is masked by coexistent dehydration. Examination of the blood reveals a normal or a slightly elevated serum protein level. The administration of fluids, particularly by the intravenous route, is promptly followed by the appearance of subcutaneous edema. At this time, examination of the blood reveals a definite lowering of the serum protein level. This group is composed of patients with diseases which interfere with the intake or absorption of proteins and of water, e. g., benign or malignant strictures of the esophagus, pyloric obstruction, severe diarrhea, or duodenal, jejunal and ileal fistulas.

TABLE 4.—*Hypoproteinemia Without Edema*

Patient and Sex	Race and Age, Yr.	Diagnosis	Serum Protein, Gm. per 100 Cc.	Type of Hypoproteinemia	Daily Fluid Intake		Daily Urinary Output, Cc.
					Oral, Cc.	Parenteral, Cc.	
J. L. ♂	W 47	Duodenal ulcer with pyloric obstruction (vomiting)	4.77	Prehepatic	1,500-2,000	1,000	1,200-1,800
A. E. ♂	W 59	Carcinoma of the small intestine (hematemesis and melena)	4.42	Prehepatic and posthepatic	2,000	.....	1,000-1,500
M. P. ♀	W 59	Dissecting aneurysm of the aorta (retroperitoneal hemorrhage; bilateral hydrothorax)	4.80	Posthepatic	.....	3,000	1,000-2,000
M. P. ♀	W 73	Carcinoma of the kidney (continuous and severe hematuria)	5.11	Posthepatic	1,000-2,000	.....	1,000-1,500

Hypoproteinemia in patients of the second group is not accompanied by edema of the subcutaneous tissues and is somewhat difficult to recognize. Its presence is suspected only when there occurs a delay in wound healing or when there are disturbances of gastrointestinal motility. Prolongation of the emptying time of the stomach may be present so that as much as 60 per cent of a barium sulfate meal may be retained six hours after ingestion. Edema of the stoma of a gastroenterostomy may lead to obstructive symptoms. Diminution of the peristalsis of the intestines may occur and, when accompanied by distention of the intestines, may closely simulate adynamic ileus. These patients frequently do not show evidences of general malnutrition. In table 4 are recorded data on a group of patients in whom hypoproteinemia was not accompanied by edema of the subcutaneous tissues. It is significant that in none of these patients were there evidences of infection. It will be noted, too, that fluid intake and output were within normal limits.

The edema which is presented by patients of group 3 renders simple the recognition of the underlying hypoproteinemia. These patients often are poorly nourished. Moreover, hypoproteinemia in this group is generally associated with one or more of the following accessory factors: tissue protein defects due to malnutrition, excessive fluid and salt intake or sepsis.

PHYSIOLOGIC ASPECTS OF THE THERAPEUTIC PROBLEM

The response to therapy of hypoproteinemia will depend to a large extent on the type, whether this is prehepatic, hepatic or posthepatic. The coexistence of a depleted reserve of plasma protein-building material as in the prehepatic type, or severe liver damage, as in the hepatic type, renders hypoproteinemia less responsive to treatment. For this reason, the posthepatic type of hypoproteinemia, e. g., that associated with burns, usually responds rapidly to treatment. The importance of the type of hypoproteinemia from the viewpoint of therapy is illustrated by the following case reports:

CASE 1.—*Hypoproteinemia—prehepatic type.*

J. L., a Negro woman aged 33 years, presented herself at Charity Hospital with a history of increasing constipation. Owing to pain associated with attempts at defecation, there had been a voluntary restriction of diet. Physical examination disclosed an extremely emaciated Negro woman with grade 4 pitting edema of the lower extremities extending to the knees. A rectal stricture which barely admitted the tip of the index finger was present. The serum protein level was 5.17 Gm. per hundred cubic centimeters, and the result of the intravenous hippuric acid test of liver function was 0.204 Gm. (normal, 0.7 Gm.). Despite blood transfusions, the serum protein level dropped to 3.93 Gm. per hundred cubic centimeters, and the edema persisted. Death resulted.

CASE 2.—*Hypoproteinemia—hepatic and posthepatic type.*

J. P., a Negro woman aged 38 years, presented herself at Charity Hospital with evidences of pelvic peritonitis which followed dilation of a rectal stricture with bougies. While she was in the hospital, the temperature ranged between 99 and 103 F. Blood examination showed increasing anemia and leukocytosis (26,500 cells). The patient became jaundiced (the icterus index was 17; the van den Bergh test had a direct delayed reaction). The serum protein level fell to 5.21 Gm. per hundred cubic centimeters. Edema of the lower extremities and the face appeared. The result of the intravenous hippuric acid test of liver function was 0.276 Gm. (normal, 0.7 Gm.). Repeated blood transfusions produced a slow rise in the serum protein level to 6.29 Gm. per hundred cubic centimeters. Coincidentally, the function of the liver improved, as indicated by the intravenous hippuric acid test, the result of which was now 0.798 Gm. The edema diminished greatly, but pitting edema of the ankles (grade 1) persisted until the temperature returned to normal, i. e., two weeks after the return of the serum protein to the normal level.

CASE 3.—*Hypoproteinemia—posthepatic type.*

A. T., a young white man aged 23 years, was severely burned on the arms and the trunk. Edema of the face and the lower extremities appeared on the third day after admission to Charity Hospital. The patient had been receiving 2,500 to

3,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride daily. The serum protein level was 4.6 Gm. per hundred cubic centimeters at this time. One transfusion of 350 cc. of ascitic fluid was given. Marked diuresis occurred. The following day the edema had disappeared, and the serum protein level had risen to 6.8 Gm. per hundred cubic centimeters. The excellent response to treatment in this patient was due to the fact that no depletion of the tissue proteins or of the protein reserve in the liver had occurred.

Edema, as well as hypoproteinemia, varies in its response to treatment. Edema which follows the administration of fluids to patients with hypoproteinemia appears to be more responsive to treatment than that which occurs spontaneously during the development of hypoproteinemia. Since the function of the liver is frequently lowered in all types of hypoproteinemia, a diet designed to protect the liver should be given. A high carbohydrate, high protein and low fat diet and the administration of solutions of dextrose by vein will be found useful.

The presence of infection offers a serious barrier to the effective treatment of hypoproteinemia and edema. Infection not only reduces the protein-regenerating ability of the liver, but it also tends to favor the formation of edema by altering the permeability of the capillaries. Hypoproteinemia in the presence of infection should be treated not by plasma, serum or ascitic fluid but by fresh whole blood, which helps the patient to combat not only hypoproteinemia but also infection.

Localized collections of pus should be opened and drained as soon as possible. The local and general use of chemotherapeutic agents, such as sulfanilamide and its derivatives is not contraindicated in infections associated with hypoproteinemia. We have used these drugs successfully in patients with hypoproteinemia. Nevertheless, caution should be exercised, since hypoproteinemia is often associated with a diminution of hepatic function and since sulfanilamide and its derivatives can exert a deleterious effect on the liver.[49]

Hypoproteinemia may be complicated by the presence of a deficiency of vitamins B_1 and C. In certain patients it is difficult to distinguish the edema of hypoproteinemia from that of beriberi. The addition of these vitamins to the diet may produce a more rapid response of hypoproteinemia to treatment.

Not infrequently patients with hypoproteinemia will exhibit evidences of severe secondary anemia, particularly if there is coexistent infection. If edema is present in such patients, it will disappear when adequate measures are taken to relieve hypoproteinemia and infection. In a small group of patients, however, edema persists until anemia is cured. This phenomenon has been observed by Salah [28] in the helminthic types of anemia.

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49. Davis, H. A.; Harris, L. C., and Schmeisser, H. C.: The Toxic Effects of Sulfanilamide upon Tissues of Rats, J. Lab. & Clin. Med. **25**:1263-1275 (Sept.) 1940.

Since operative intervention is frequently necessary, the use of anesthesia in patients with hypoproteinemia must be discussed. It has been conclusively demonstrated by many workers that both general and spinal anesthesia affect liver function adversely. Since the function of the liver is usually diminished in hypoproteinemic states, general and spinal anesthesia carry an increased hazard. Thus, it has been shown that preliminary damage of the liver by chloroform renders animals susceptible to "hypoproteinemic" shock produced by plasmapheresis.[39] The conclusion is obvious that every effort must be made to rectify hypoproteinemia and to restore the functional ability of the liver in operative patients before subjecting them to either general or spinal anesthesia.

The factors affecting the response of the patient with hypoproteinemia to treatment can now be summarized as follows:

Favorable Factors:

1. Amenability of the underlying causative condition to treatment.
2. Normal liver function or, alternatively, reduction of liver function due to hypoproteinemia alone.
3. Short duration of hypoproteinemia, since this would indicate the probable existence of reserves of whole proteins and precursors of protein in the liver.
4. Absence of tissue protein defect.
5. Absence of subcutaneous edema or, if present, short duration of subcutaneous edema.

Unfavorable Factors:

1. Lack of amenability of the underlying causative condition to treatment.
2. Reduction of liver function due to causes other than hypoproteinemia itself.
3. Prolonged duration of the hypoproteinemic state prior to treatment.
4. Presence of tissue protein defect.
5. Presence of subcutaneous edema, especially if this is prolonged.
6. Presence of infection.
7. Presence of accessory nutritional deficiency, e. g., beriberi, pellagra.

A paradoxic problem from the viewpoint of therapy is presented by the concurrence of edema and dehydration in patients with hypoproteinemia, in whom attempts to relieve the dehydration result in an increase of the edema. In such patients, treatment should be directed toward hypoproteinemia rather than toward either dehydration or edema, which can be temporarily neglected. The transfusion of plasma, serum or ascitic fluid increases the osmotic pressure of the blood, and fluid is withdrawn from the edematous areas into the blood stream and distributed more equally to the other body tissues.

PROTEIN REPLACEMENT BY THE PARENTERAL ROUTE

The principles underlying the dietary treatment of hypoproteinemia have already been discussed. However, in most patients it is necessary to administer additional proteins or amino acids by the parenteral route.

The forms of protein and amino acids which are available for parenteral use are: (1) whole blood; (2) blood plasma (whole or lyophilized); (3) blood serum (whole or lyophilized); (4) ascitic fluid; (5) digests of casein.

The effects of serum transfusion in nutritional edema in dogs have been studied.[50] It was found that no significant changes in the amount of edema occurred, despite a definite elevation in the total amount of albumin and globulin in the blood. There was an increase in the blood volume after serum transfusion. This increase was greater than the amount of serum transfused, and Weech and co-workers therefore suggested that water passed from the interstitial tissue spaces into the blood. It is significant that despite the augmentation of the serum proteins, no change in edema occurred.

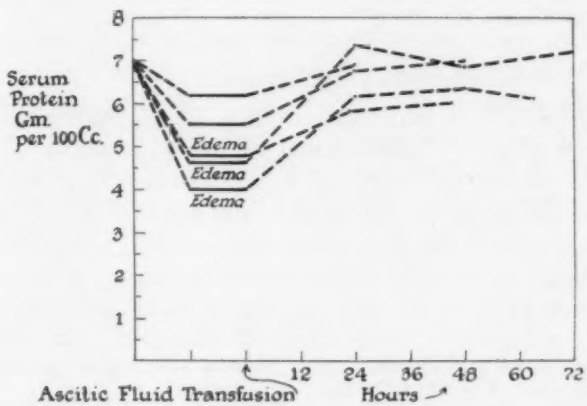

Chart 2.—Effect of the transfusion of ascitic fluid in patients with hypoproteinemia.

Ascitic fluid may be administered either intravenously or subcutaneously in states of hypoproteinemia. The results in several patients are illustrated in chart 2. Ascitic fluid may be administered without preliminary typing or cross matching.[51] The methods of collection and storage of this fluid have been described previously.[52] Digests of

50. Weech, A. A.; Goettsch, E., and Reeves, E. B.: The Effect of Serum Transfusion on the Plasma Protein Depletion Associated with Nutritional Edema in Dogs, J. Clin. Investigation **12**:217-227 (Jan.) 1933.

51. Davis, H. A.: The Inactivation of Group-Specific Isoagglutinins in Relation to the Transfusion of Incompatible Plasma, Serum and Ascitic Fluid, Surgery **10**:592-603 (Oct.) 1941.

52. Davis, H. A., and White, C. S.: Human Ascitic Fluid as a Blood Substitute in Experimental Secondary Shock, Proc. Soc. Exper. Biol. & Med. **38**:462-465 (May) 1938. Davis, H. A., and Blalock, J. F.: Autologous and Homologous Transfusion of Human Ascitic Fluid, J. Clin. Investigation **18**:219-224 (March) 1939.

casein have been used successfully to maintain nitrogen equilibrium when administered by vein [53] and subcutaneously.[54] Recently it was shown that papain digests of casein given intravenously or subcutaneously stimulate new plasma protein production as effectively as protein given by mouth.[55] It must be remembered, however, that the administration of amino acids, as various groups of workers have suggested, will be effective only if the liver is capable of protein synthesis.

Vitamin C should be administered with such mixtures of amino acids, since recent work [56] appears to indicate that this vitamin is essential for the proper metabolism of certain amino acids, namely, phenylalanine and tyrosine.

The treatment of edema associated with nephrosis by the intravenous injection of solutions of acacia has been suggested.[57] However, it has been demonstrated that the injection of acacia interferes with protein regeneration by the liver.[58]

CONCLUSIONS AND SUMMARY

A new classification of hypoproteinemia as prehepatic, hepatic and posthepatic is proposed. The causation of hypoproteinemia and the physiologic and pathologic effects of hypoproteinemia are discussed. The relation of the serum protein level to the function of the liver is considered. It is pointed out that these different forms of hypoproteinemia vary in their responses to treatment. The results of the transfusion of ascitic fluid in hypoproteinemia are reviewed.

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53. Elman, R.: Parenteral Replacement of Protein with the Amino-Acids of Hydrolyzed Casein, Ann. Surg. **112**:594-602 (Oct.) 1940.

54. Altshuler, S. S.; Hensel, H. M., and Sahyun, M.: Maintenance of Nitrogen Equilibrium by Amino Acids Administered Parenterally, Am. J. M. Sc. **200**:239-244 (Aug.) 1940.

55. Madden, S. C.; Zeldis, L. J.; Hengerer, A. D.; Miller, L. L., and Whipple, G. H.: A Casein Digest by Vein Utilized to Form Blood Plasma Protein, Science **93**:330-331 (April 4) 1941.

56. Levine, S. Z.; Marples, E., and Gordon, H. H.: A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: I. Identification in Assay of Intermediary Products, J. Clin. Investigation **20**:199-207 (March) 1941. Levine, S. Z.; Gordon, H. H., and Marples, E.: A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: II. Spontaneous Occurrence and Eradication by Vitamin C, ibid. **20**:209-219 (March) 1941.

57. Hartmann, A. F.; Senn, M. J. E.; Nelson, M. V., and Perley, A. M.: The Use of Acacia in the Treatment of Edema, J. A. M. A. **100**:251-254 (Jan. 28) 1933.

58. Andersch, M., and Gibson, R. B.: Studies on Effects of Intravenous Injections of Colloids: Deposition of Acacia in Liver and Other Organs and Its Excretion in Urine and Bile, J. Pharmacol. & Exper. Therap. **52**:390-407 (Dec.) 1934.

CHANGES IN THE BLOOD AND THE COMPOSITION OF THE PERITONEAL EXUDATE IN INDUCED SPREADING PERITONITIS

A PRELIMINARY REPORT

J. O. BOWER, M.D.

L. A. TERZIAN, Sc.D.

AND

A. E. PEARCE, M.D.

PHILADELPHIA

Death from appendicitis-peritonitis is one of the major problems of medicine and surgery today, and the condition ranks ninth among the principal causes of death. Appendicitis-peritonitis is the cause of over 92 per cent of so-called deaths from appendicitis, and the mortality rate throughout the United States is approximately 33 per cent. The results of a workable proved plan for reduction of the mortality rate have been published elsewhere.[1]

A study of appendicitis-peritonitis induced in the dog, investigations of blood and other body fluids in our own patients and a study of the reaction of 10,306 patients to appendicitis-peritonitis (26 per cent of 39,087 patients with acute appendicitis admitted to 181 hospitals in Pennsylvania over a period of ten years) together indicate that several factors, namely, leukocytosis, the cementing together of loops of intestine by plastic exudate, the migration of the omentum and the presence or absence of antibodies, are responsible for recovery or death of both man and dog.

Delay in hospitalization and the administration of laxatives in an attack of appendicitis are causes of appendicitis-peritonitis, and in man with this disease and in the dog suffering from experimentally induced spreading peritonitis, death results from similar causes. Body fluid changes occurring in both man and dog with appendicitis-peritonitis are important not only from the standpoint of the management of the disease

From the Foundation for Clinical and Surgical Research and the Division of Biochemistry of the Laboratories of the Philadelphia General Hospital.

1. Bower, J. O.: Spreading Peritonitis Complicating Acute Perforative Appendicitis: Routine Operations Versus Scientific Management, J. A. M. A. **112**:11-17 (Jan. 7) 1939; Report of the First State-Wide Survey of Acute Appendicitis Mortality, Pennsylvania M. J. **43**:1145-1174 (May) 1940.

but also because they reveal other changes which indicate to some degree how defensive mechanisms operate.

Comparative analyses of the peritoneal exudate obtained from human patients with peritonitis and from dogs with experimental peritonitis shown in table 1 suggest that similar pathologic and physiologic reactions have taken place. The data presented in table 1 indicate that the fluid obtained from the peritoneal cavity of these subjects contains large amounts of plasma protein. As will be shown later, in the experiments

TABLE 1.—*Comparison of the Constituents of Blood and Peritoneal Exudate of Man and of Dog* *

Subject	Pathologic Condition		Hematocrit Value	Total Protein	Albumin	Albumin-Globulin Ratio	Chloride
		A. Man.					
B. D.	Acute catarrhal appendicitis	Blood	....	7.5	5.2	2.2	...
		Peritoneal exudate	....	5.7	4.1	2.5	...
E. K.	Appendix gangrenous, serous coat intact	Blood	....	7.0	4.5	1.8	575
		Peritoneal exudate	....	6.3	4.5	2.3	545
V. K.	Spreading peritonitis, perforated duodenal ulcer	Blood	47.5	6.6	3.7	1.3	605
		Peritoneal exudate	....	3.8	2.4	1.7	645
		B. Dog					
39	Appendix gangrenous, localizing process	Blood	....	7.1	4.1	1.4	670
		Peritoneal exudate	....	6.2	3.8	1.6	655
93	Appendix gangrenous, localizing process	Blood	....	7.7	4.2	1.2	620
		Peritoneal exudate	....	7.0	4.2	1.5	620

* This table shows not only the close approximation of the protein content of the blood and the peritoneal exudate in man and dog but also an increase in these with each advanced step of the disease (compare analysis of dog 39 with first analysis in table 2). An exception to this was the peritoneal exudate associated with perforated duodenal ulcer; in this case the quantity of fluid was excessive and probably accounted for the comparatively low protein content of both blood and peritoneal exudate. The localizing process referred to is an early perforation of a gangrenous appendix in the process of being walled off from the general peritoneal cavity by loops of intestine and omentum cemented together with plastic exudate. Free in the general peritoneal cavity in both man and dog will be found a varying amount of bacteria-free peritoneal exudate.

described in this paper, these changes have an important relation to the course of the infection.

EXPERIMENTAL METHODS

Adult mongrel dogs weighing an average of 16 Kg. and in a good nutritional state were used. In every instance control blood examinations were made prior to the experimental production of peritonitis.

Laboratory Methods.—(*a*) Plasma volume and blood volume were estimated according to a modification of the method outlined by Gibson and Evans,[2] using the dye T 1824. Blood samples were taken either by vein or by cardiac puncture, and the concentration of the dye was estimated by means of a Summerson photo-

2. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of Blood Volume: Changes in Blood Volume, Venous Pressure and Blood Velocity Rate in Chronic Congestive Heart Failure, J. Clin. Investigation **16**:851-858 (Nov.) 1937.

electric colorimeter. It was found that error due to hemolysis or lactescence could be overcome by treating the plasma with acetone. Dye concentrations were measured in the clear fluid remaining after centrifugation. Details will be reported in a separate paper.

(*b*) Determinations of total protein and albumin were made according to the methods described by Kingsley,[3] globulin being calculated by difference. Total circulating protein was calculated from plasma volume and grams of protein per cubic centimeter. As will be reported elsewhere, in some few cases there were certain differences between biuret protein and protein as determined by the Kjeldahl method. These differences, however, were not of sufficient magnitude to affect the results in this series of experiments.

(*c*) Determinations of hemoglobin were done by the method of Sanford, Sheard and Osterberg.[4] For determination of red blood cell volume, Sanford-Magath hematocrit tubes were used, and the sample was centrifuged at 3,000 revolutions per minute for thirty minutes. Heparin was used as an anticoagulant.

(*d*) Chloride was determined by the method of Van Slyke.

Operative Technic.—Prior to operation small doses of morphine and atropine were administered subcutaneously. Anesthesia induced with ether and aseptic technic were employed.

Spreading peritonitis was induced according to the procedure described by Bower, Burns and Mengle.[5] The appendix and its mesentery, together with all its blood vessels, were ligated, and the appendix was traumatized. In one series, 60 to 90 cc. of castor oil, varied according to the weight of the animal, was administered by catheter immediately after operation.

Management.—During the first series of experiments water was usually given to the animals twelve or fourteen hours after operation, but because persistent vomiting occurred, especially in those dogs given castor oil, water was subsequently withheld for forty-eight hours from dogs treated with castor oil, and for at least twenty-four hours from dogs not receiving castor oil.

EXPERIMENTAL OBSERVATIONS

Series 1 (Ligation of the appendix and its mesentery and administration of castor oil).—Table 2 presents data obtained from the first series of animals in which the appendix and its mesentery were ligated and castor oil was administered. In each case within twenty-four to forty-eight hours after operation, during which time spreading peritonitis developed, there was considerable rise in the total protein and albumin, accompanied by a rise in the hematocrit value. Considerable depletion of chloride occurred. This was most marked in the animals that vomited.

3. Kingsley, G. R.: The Determination of Serum Total Protein, Albumin and Globulin by the Biuret Reaction, J. Biol. Chem. **131**:197-200 (Nov.) 1939; A Rapid Method for the Separation of Serum Albumin and Globulin, ibid. **133**:731-735 (May) 1940.

4. Sanford, A. H.; Sheard, C., and Osterberg, A. E.: Photelometer and Its Use in the Clinical Laboratory, Am. J. Clin. Path. **3**:405-420 (Nov.) 1933.

5. Bower, J. O.; Burns, J. C., and Mengle, H. A.: Spreading Peritonitis Complicating Acute Perforative Appendicitis, Arch. Surg. **37**:751-759 (Nov.) 1938.

The initial increase in concentration of plasma protein and red blood cells was followed by anemia and hypoproteinemia. The initial increase in protein and red blood cell concentration suggested considerable dehydration accompanied by hemoconcentration, and, in spite of apparently rising protein values, a probable loss of plasma proteins. Although it was obvious from these data that fluid loss had taken place, it was impossible to measure the actual severity of the losses from these determinations alone. For this reason blood volume studies were undertaken.

Blood volume determinations were made twenty-four and forty-eight hours after operation and at various intervals thereafter until the plasma

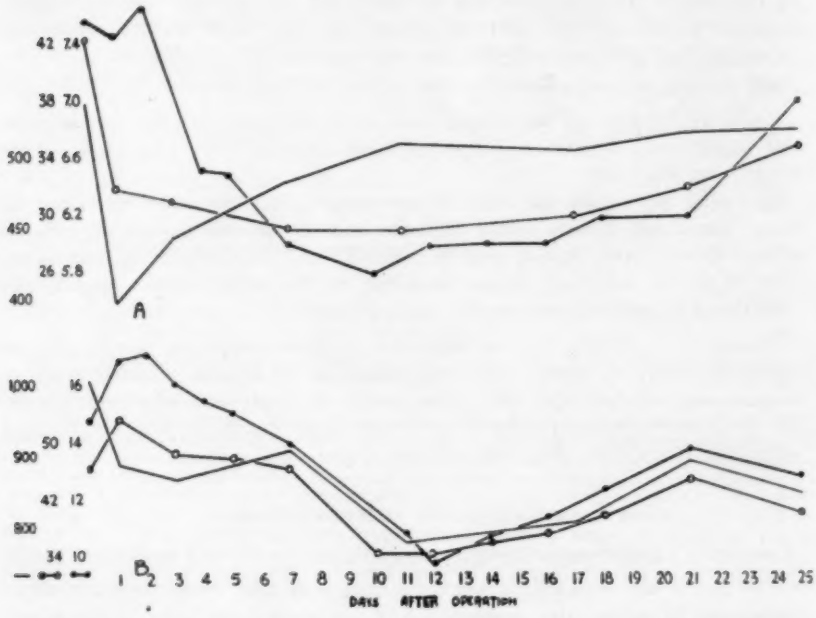

Chart 1 (dog 24).—Chart showing the effects of ligation of the appendix and its mesentery with postoperative administration of castor oil: *A*, changes in protein and in plasma volume over a period of twenty-five days following experimentally induced peritonitis; *B*, changes in hemoglobin, hematocrit value and blood volume over the same period. In *A*, the black line represents the plasma volume (cubic centimeters); the line with the open circles, the total circulating plasma protein (grams); the line with the black dots, the protein per hundred cubic centimeters of plasma (grams). In *B*, the black line represents the blood volume (cubic centimeters); the line with the open circles, the per cent red blood cell volume; the line with the black dots, the hemoglobin per hundred cubic centimeters of blood (grams).

volume had returned to normal or nearly normal values. The resulting changes following operation in total circulating protein, plasma volume and per cent red blood cell volume are presented in chart 1 and table 2. In each dog within twenty-four to forty-eight hours after operation, there

was considerable fall in plasma volume, a decrease in the amount of circulating protein, and, concurrent with the plasma losses, an increase in concentration of the cellular elements of the blood as evidenced by the

TABLE 2.—*Blood Changes During the Course of Experimental Peritonitis Induced by Ligation of the Appendix with Postoperative Administration of Castor Oil*

Dog		Normal	Days After Operation 1	2	3	4	5	6	7	8	9	10	Plasma Loss, %	Protein Loss, %
3	Total protein.....	7.3	8.05	7.8	6.5	6.5	6.3	6.3	6.0	6.0	5.9	6.2	....	....
	Hematocrit value...	46.5	53.4	47.8	45.0	42.4	37.0	33.2	32.5	30.0	28.8	34.0	....	....
	Chloride.....	670	670	670*	595	570	550	605	645	...	650	...	....	....
4	Total protein.....	5.7	6.5	7.1	6.2	6.2	5.6	5.4	5.2	5.2	5.2	5.3	....	....
	Hematocrit value...	46.0	48.5	47.5	43.2	43.1	41.5	37.3	37.2	36.1	35.6	35.0	....	....
	Chloride.....	650	650	655*	585*	600	585	640	635	...	...	...	....	....
5	Total protein.....	6.2	7.2	7.8	7.5	Died								
	Hematocrit value...	49.0	61.2	61.4	61.4									
	Chloride.....	675	655	675*	505									
9	Total protein.....	6.0	6.7	Died										
	Hematocrit value...	48.8	64.2											
	Cholride.....	675	610*											
10	Total protein.....	6.0	6.8	6.0	5.8	5.6	4.8	5.2	5.4	6.0	...	...	....	....
	Hematocrit value...	50.2	61.3	60.2	52.1	50.1	43.0	41.0	42.0	42.5	...	....	....	....
	Chloride.....	650	650*	565	545	550	630	670	665	...	...	...	....	....
18	Total protein.....	6.0	7.7	Died										
	Hematocrit value...	56.0	69.0											
	Chloride.....	655	645											
19	Total protein.....	5.4	6.3	7.0	Died									
	Hematocrit value...	42.5	50.3	46.5										
	Chloride.....	655	630	605										
16	Plasma volume.....	500	...	395	...	415	...	...	445	...	...	...	21.0	....
	Total circulating protein.....	29.5	....	25.6	....	26.9	....	....	25.8	....	....	....	....	13.5
	Hematocrit value...	45.0	52.5	50.0	46.0	46.0	....	45.0	40.5	....	....	....	....	....
	Chloride.....	635	620	595	630	640	...	590	615	...	...	...	....	....
17	Plasma volume.....	540	405	...	495	...	...	...	560	...	...	...	25.0	....
	Total circulating protein.....	31.8	27.0	....	30.6	....	....	....	32.3	....	....	....	....	12.2
	Hematocrit value...	46.0	50.0	55.1	52.3	48.2	....	46.4	37.0	....	....	....	....	....
	Chloride.....	645	645*	635	590	605	...	595	560	...	...	...	....	....
20	Plasma volume.....	825	720	Died	...	...	...	...	...	...	...	...	12.5	....
	Total circulating protein.....	48.0	44.0	....	....	....	....	....	....	....	....	....	....	8.5
	Hematocrit value...	48.5	56.5											
	Chloride.....	640	640											
23	Plasma volume.....	685	...	525	Died	...	...	...	...	...	...	...	23.2	....
	Total circulating protein.....	42.5	....	35.7	....	....	....	....	....	....	....	....	....	16.0
	Hematocrit value...	50.9	58.0	57.7	59.0									
	Chloride.....	640	640*	655	670*									
24	Plasma volume.....	540	405	...	445	...	...	...	480	...	...	...	26.0	....
	Total circulating protein.....	42.6	32.0	31.1	....	....	....	....	29.2	....	....	....	....	25.0
	Hematocrit value...	46.0	53.8	53.3	49.0	49.5	48.5	....	46.7					
	Chloride.....	650	645	640	600	540	530	...	570					
	Average.....												21.5	14.9

* Vomiting occurred.

rise in hematocrit value and in hemoglobin. Since the hematocrit value was found to parallel the hemoglobin concentration, the latter is not included in the table or the chart. In addition there was considerable

depletion of plasma chloride unrelated to vomiting, although losses of chloride were most marked when vomiting occurred. This is shown by the decrease which took place in dog 24.

Reference to table 2 will show that there was considerable variation in the extent of the loss of plasma and protein and in the individual reactions of the animals to the infection. In this series no relation could be shown between the extent of the loss of protein and plasma and the probable recovery or death of the animal. For example, dog 20 suffered a loss in plasma volume of 12.5 per cent and a loss of protein of only 8.5 per cent, yet it failed to survive. Dog 23 showed losses of 23.2 per cent and 16.0 per cent, and it, too, failed to survive. On the other hand, dog 24, which showed much greater losses in protein but a somewhat lesser loss in plasma volume, recovered in time, and dogs 16 and 17, which showed much greater changes than dog 20, also recovered. Although considerable losses in plasma and protein occur during the course of spreading peritonitis and although the degree of these losses determine to some extent the survival of the animals, in this particular series it seems that other factors, viz., leukocytosis and omental migration, also played a significant part.

Chart 1 shows in greater detail the changes taking place over an extended period in dog 24. The significant features are the drop in plasma volume and in the total circulating protein twenty-four hours after operation. In this particular animal, the plasma volume dropped from a normal value of 540 to 405 cc., while the total circulating protein dropped from 42.6 to 32.0 Gm. Two other features are to be noted: (1) the lengthy period of hypoproteinemia, indicating that once protein reserves have been seriously depleted, resynthesis of sufficient protein with recovery to the normal level is attended with considerable difficulty and (2) the extended period of time required by the animal to reestablish normal plasma volume. As plasma volume is restored, red blood cell formation fails to keep pace, and anemia becomes apparent and persists over a considerable period. In almost all cases the period of convalescence is characterized by long-standing anemia. It is of interest to note also that protein levels alone constitute an inaccurate index of the actual quantity of circulating protein and that it is only when plasma volume has been reestablished to some extent that the concentration of plasma protein approximates a true indication of the amount of protein present.

Chart 1 *B* represents the changes in hemoglobin, per cent red blood cell volume and total blood volume. The changes in this case parallel the changes demonstrated in chart 1 *A*. Coincident with the loss of plasma there was an increased concentration of the cellular elements and the hemoglobin, while the blood volume itself decreased 11.3 per cent in twenty-four hours.

Series 2 (Ligation of the appendix and its mesentery with no administration of castor oil).—Data for the series of animals in which the appendix and its mesentery were ligated and castor oil was not admin-

TABLE 3.—*Blood Changes During the Course of Experimental Peritonitis Induced by Ligation of the Appendix Without Postoperative Administration of Castor Oil*

Dog		Normal	Days After Operation 1	2	3	4	5	6	7	Plasma Loss, %	Protein Loss, %
25	Total protein	7.5	7.5	8.35	Died						
	Hematocrit value	35.0	40.5	49.3							
	Chloride	620	610	620							
26	Total protein	6.6	6.8	Died							
	Hematocrit value	52.0	62.8								
	Chloride	635	610								
27	Total protein	6.2	6.5	Died							
	Hematocrit value	42.2	48.8								
	Chloride	620	...								
31	Total protein	6.3	6.6	Died							
	Hematocrit value	44.6	57.2								
	Chloride	640	...								
32	Total protein	6.2	6.5	7.1	Died						
	Hematocrit value	52.3	59.4	71.4							
	Chloride	645	640	...							
21	Plasma volume	710	550	...	595	...	685	...	...	22.5	....
	Total circulating protein	42.6	34.5	....	32.0	....	37.0	....	....	....	19.0
	Hematocrit value	51.8	61.3	56.2	52.5	51.6	43.6	....	42.3		
	Chloride	645	645	670	650	660	640	...	635		
22	Plasma volume	545	...	415	...	510	...	...	...	23.9	....
	Total circulating protein	33.8	....	28.2	....	35.0	....	....	....	....	16.3
	Hematocrit value	50.0	51.3	55.6	51.6	51.0					
	Chloride	630	615	615	605	600					
28	Plasma volume	580	415	...	430	...	...	560	...	28.5	....
	Total circulating protein	42.3	32.0	....	27.1	....	....	30.2	....	....	25.5
	Hematocrit value	50.0	54.2	56.9	52.5	50.2	....	40.3	37.1		
	Chloride	640	...	615	...	605	...	...	635		
29	Plasma volume	685	420	Died	...	...	...	...	...	38.7	....
	Total circulating protein	44.5	31.0	....	....	....	....	....	....	....	30.5
	Hematocrit value	49.8	58.3	61.2							
	Chloride	630	...	635							
30	Plasma volume	545	...	385	...	410	Died	...	...	29.5	....
	Total circulating protein	33.8	....	28.5	....	29.0	....	....	....	....	15.6
	Hematocrit value	45.5	53.0	58.0	54.5	51.5					
	Chloride	645	...	645	...	665					
35	Plasma volume	880	...	695	...	915	...	...	915	21.0	....
	Total circulating protein	52.0	....	43.2	....	48.5	....	....	50.3	....	17.2
	Hematocrit value	46.0	46.0	48.2	41.0						
	Chloride	645	640	640	...	610	...	...	650		
37	Plasma volume	945	710	...	775	...	...	...	775	25.0	....
	Total circulating protein	59.6	46.5	....	42.6	....	....	....	44.2	....	20.2
	Hematocrit value	48.8	55.2	47.0	45.6	41.6	....	....	36.6		
	Chloride	665	615	620	...	610	...	...	650		
	Average									27.0	20.6

istered are presented in table 3. The changes parallel those which occurred in the animals given castor oil except that in this particular series the plasma volume and total circulating protein losses were some-

what greater—average losses of 27.0 and 20.6 per cent, respectively, as compared with 21.5 and 14.9 per cent in the animals given castor oil. There was considerable variation in the size of the appendix in different animals, and it is possible that dogs with comparatively larger ceca were more severely traumatized by the operation and as a consequence suffered a more severe reaction. Further, the amount of manipulation necessary to deliver the organ was undoubtedly responsible in some degree for the extent of reaction in the animal. However, both series were too small to enable one to draw any positive conclusions, and with so many factors involved it would be difficult to ascribe the degree of the changes to any one particular cause.

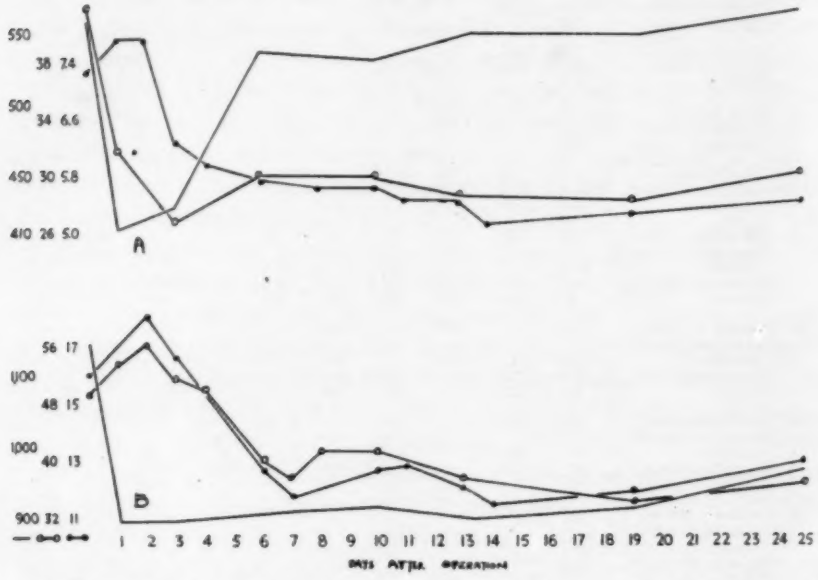

Chart 2 (dog 28).—Chart showing the effect of ligation of the appendix and its mesentery without the postoperative administration of castor oil: *A*, changes in protein and in plasma volume over a period of twenty-five days following experimentally induced peritonitis; *B*, changes in hemoglobin, hematocrit value and blood volume over the same period of time. In *A*, the black line represents the plasma volume (cubic centimeters); the line with the open circles, the total circulating plasma protein (grams); the line with the black dots, the protein per hundred cubic centimeters of plasma (grams). In *B*, the black line represents the blood volume (cubic centimeters); the line with the open circles, the per cent red blood cell volume; the line with the black dots, the hemoglobin per hundred cubic centimeters of blood (grams).

There is, nevertheless, one difference between this group and the group given castor oil; animals not given castor oil that survived were able to restore the plasma volume to normal levels within a comparatively

shorter period. Animals not given castor oil are usually able to retain fluids twenty-four hours after operation, while animals which have received castor oil vomit persistently for several days thereafter, thereby precluding the possibility of any appreciable amount of fluid intake by mouth. This may explain in part why restoration of plasma volume is more rapid in animals not given castor oil. Dog 37 constitutes a notable exception in that it failed to recover its normal plasma volume. The probable explanation may lie in the fact that this animal suffered persistent diarrhea from the fifth day on and finally had to be discarded for that reason. Graphic representation of the course of dog 28 in chart 2, which was typical of the group as a whole, brings out these features more clearly. Twenty-four hours after operation there was a

TABLE 4.—*Blood Studies of Animals Killed at Various Intervals After Ligation of the Appendix and the Production of Peritonitis*

Dog	Hematocrit Value	HbO_2	Total Protein	Albumin	A'bumin-Globulin Ratio	Chloride	Carbon Dioxide	Plasma Volume	Total Circulating Protein
39 Normal.....	44.0	11.9	6.0	3.9	1.8	670	38	780	46.8
24 hr. after operation.....	63.5	17.9	7.1	4.1	1.4	670	36	520	36.9
Peritoneal fluid..	....	....	6.2	3.8	1.6	655	29	...	....
42 Normal.....	55.0	16.9	7.0	3.7	1.1	645	..	685	48.0
48 hr. after operation.....	66.1	21.0	7.9	3.6	0.86	615	..	530	41.8
Peritoneal fluid..	....	....	6.5	3.5	1.1	650	..	...	....
43 Normal.....	45.0	14.5	7.1	4.0	1.3	655	36	600	....
24 hr. after operation.....	53.5	16.4	7.7	4.2	1.2	620	35	560	....
Peritoneal fluid..	....	....	7.0	4.2	1.5	620	24	...	....

28.5 per cent loss in plasma volume, with an attendant decrease of 25.5 per cent in total circulating protein. However, in this case, the animal was able to restore its plasma volume to almost normal levels within six to seven days. As a consequence of the more rapid restoration of plasma volume, the resulting anemia became apparent earlier in the course of the disease and was conspicuous throughout the period of recovery.

Series 3 (Animals killed at intervals following operation).—The purpose of the series of experiments in which the animals were killed at intervals after operation was to determine the fate of the fluid lost from the vascular system. After ligation of the appendix without postoperative administration of castor oil, dogs were killed at various intervals. Blood samples were taken, blood volume determinations were made, and the animals were killed and immediately subjected to autopsy. The results of these studies are summarized in table 4. All the animals showed acute spreading peritonitis. Gross perforation had occurred in

dog 42, but fecal material was present only in a localized area around the lesion which already had been walled off and sealed in to some extent by loops of the intestine. In each case there was present in the peritoneal cavity a considerable amount of serosanguineous fluid which was sponged out and measured. Centrifugation of this yielded a clear plasma-like supernatant fluid. Analysis yielded the result shown in table 4, indicating that the major part of the fluid and protein losses from the vascular system could be accounted for by the fluid present in the peritoneal cavity. One would expect the smaller-sized albumin molecules

TABLE 5.—*Blood Changes in Normal Dogs Following Laparotomy*

Dog		Normal	Days After Operation 1	2	3	4	5	6	7	Plasma Loss, %	Protein Loss, %
33	Plasma volume	790	...	700	...	...	730	...	780	11.5	....
	Total circulating protein	51.0	....	46.3	....	....	48.8	....	53.0	....	9.0
	Hematocrit value	46.3	46.5	44.7	44.5	39.2	38.8	....	39.6		
	Chloride	640	635	635	635	650	650	...	650		
34	Plasma volume	745	720	...	685	...	710	...	750	3.5	....
	Total circulating protein	42.5	41.2	....	39.5	....	40.4	....	42.8	....	3.3
	Hematocrit value	39.6	40.0	40.5	38.0	37.5	38.9	....	38.0		
	Chloride	635	620	635	625	635	650	...	655		
36	Plasma volume	830	...	785	...	785	...	...	850	5.5	....
	Total circulating protein	58.2	....	53.5	....	52.0	....	....	56.5	....	8.0
	Hematocrit value	42.5	46.2	46.0	43.0	45.7	45.0	....	43.0		
	Chloride	645	640	635	...	615	...	...	635		
38	Plasma volume	775	755	...	735	...	...	...	735	3.6	....
	Total circulating protein	44.5	43.0	....	41.8	....	....	....	41.2	....	3.3
	Hematocrit value	53.0	53.0	55.2	53.0	46.5	45.0	....	44.2		
	Chloride	665	640	640	640	635	...	...	650		
	Average									6.0	5.9

to leak out more quickly than the globulin, and this is borne out by the fact that the albumin-globulin ratio of the peritoneal fluid was higher than that of the plasma with corresponding lowering of the normal plasma ratio.

Series 4 (control series).—To rule out the effects of operation alone, laparotomies were performed on a group of animals under conditions as nearly identical to the original operations as possible except, of course, that the appendix was not ligated. In each case the animals were prepared for operation as described and held under ether anesthesia; the viscera were manipulated in the manner required for the actual operation. The results in this series of animals are presented in table 5. All animals survived the operation. Although there were losses in plasma volume and circulating proteins averaging 5.9 and 6.0 per cent.

respectively, in twenty-four to forty-eight hours, the magnitude of the changes is not comparable to the extensive losses taking place in experimentally induced peritonitis. Further, with the exception of dog 38, in which a draining abscess developed at the site of incision, all the animals were able to recover their plasma volume and protein losses within five or six days.

As an additional control, water was withheld from 1 animal for a period of forty-eight hours, during which time volume studies were done. The loss in plasma volume at the end of forty-eight hours due to dehydration amounted to 5.5 per cent of the normal volume, indicating that although deprivation of water in the postoperative management of the animals is an additional factor responsible for changes in blood volume, such treatment alone cannot account for the marked changes which take place during the course of peritonitis.

COMMENT

The results reported in this paper indicate that there are produced in experimental peritonitis profound changes in the quantity and the distribution of body fluid. There is a decrease in plasma volume, a decided loss of circulating plasma proteins, an increase in the concentration of the cellular elements and a loss of plasma electrolytes. These changes resemble those preceding or accompanying shock, resulting from extensive operations, severe injuries and infections. The operation itself and the traumatization of the cecum are undoubtedly factors contributing to the fluid losses, but the induced spreading peritonitis appears to be the factor mainly responsible for the radical changes which take place and which result in the serious alterations in the blood. It is not the purpose of this paper to inquire as to the probable mechanisms responsible for producing the conditions of shock but rather to emphasize the fact that there are associated with spreading peritonitis changes similar to those of shock.

Although the systemic reactions of these animals were of varying degrees of severity, they were in general similar to those reported by Evans,[6] who produced shock in dogs by strangulating a short loop of the terminal ileum. Here again, as in traumatic shock, plasma loss appears to be local.[7]

There has been considerable criticism of the dye method for estimating blood volume on the grounds that during the conditions of shock the dye rapidly diffuses out of the blood system, thereby producing serious errors

6. Evans, E. I.: The Mechanism of Shock in Intestinal Strangulation, Am. J. Physiol. **133**:P271 (June) 1941.

7. Blalock, A.: Principles of Surgical Care, Shock and Other Problems, St. Louis, C. V. Mosby Company, 1940. Harkins, H. N.: Recent Advances in the Study and Management of Traumatic Shock, Surgery **9**:607-655 (April) 1941.

in results. In the group of animals killed at various intervals after operation, T 1824 was injected intravenously one half to three quarters of an hour prior to autopsy. Colorimetric examination of the centrifuged fluid derived from the peritoneal cavity failed to reveal the presence of dye. This suggests that the capillaries were still selectively impermeable to the dyestuff circulating in the blood system at least with regard to diffusion into the peritoneal cavity.

CONCLUSIONS

Following experimental peritonitis there is a loss of plasma volume and of blood volume with attendant loss of plasma protein and electrolyte.

Fluid present in the peritoneal cavity contains large amounts of plasma protein and accounts for much of the plasma loss.

Dependent on the degree of plasma loss there is an increase in the concentration of the cellular elements of the blood.

The most acute changes occur within twenty-four to seventy-two hours after operation. Following this critical stage of the infection there is an extended period of anemia during convalescence.

Accompanying preperforative appendicitis, appendicitis-peritonitis and spreading peritonitis from other causes in man there are varying amounts of fluid present in the peritoneal cavity containing large amounts of plasma protein and electrolytes.

Drs. J. H. Clark and J. G. Reinhold, of the Philadelphia General Hospital, gave cooperation in this study.

ESOPHAGEAL DIVERTICULA

J. DEWEY BISGARD, M.D.
OMAHA

The relative merits of the one stage and the two stage operation for the cure of esophageal diverticula have been discussed at length by many advocates of both methods. It is mutually agreed that the only deterrent of the one stage operation is the hazard of soiling the fascial spaces with the dire consequences of unlimited infection. The two stage operation

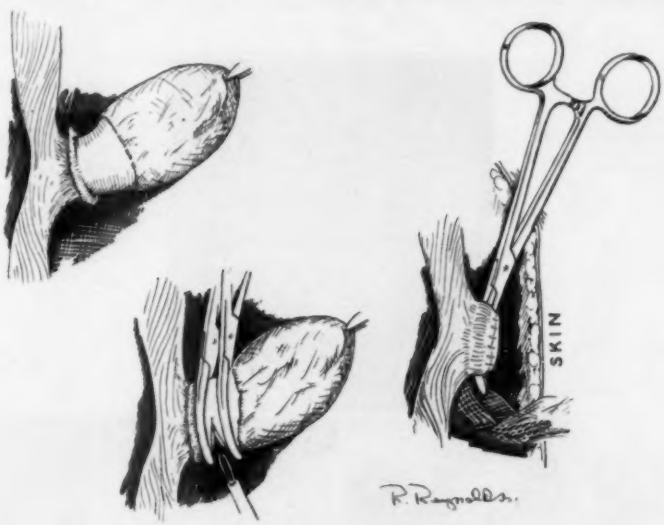

Fig. 1.—The principle of the Maxeiner operation.

permits of walling off these spaces before soiling can occur, and it is the majority surgical opinion that this factor of safety outweighs the disadvantages of the more prolonged and cumbersome procedure.

In 1939, Maxeiner [1] reported an operation performed in one stage which he stated "possesses all of the merits of the two stage operation, most important of which is elimination of wound contamination and infection but which may be accomplished by a single operation."

In principle, the operation is an aseptic resection accomplished by division of the neck of the diverticulum between hemostats with a

1. Maxeiner, S. R.: The Present Surgical Management of Esophageal Diverticula with Presentation of a New (?) Method, Tr. West. S. A. **49**:365, 1939.

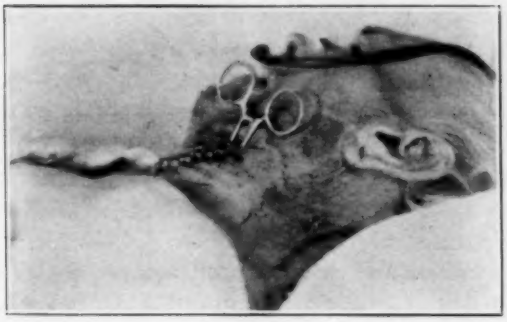

Fig. 2 (case 3).—Five days after operation. The hemostat and the Levine tube for direct gastric feedings are still in place.

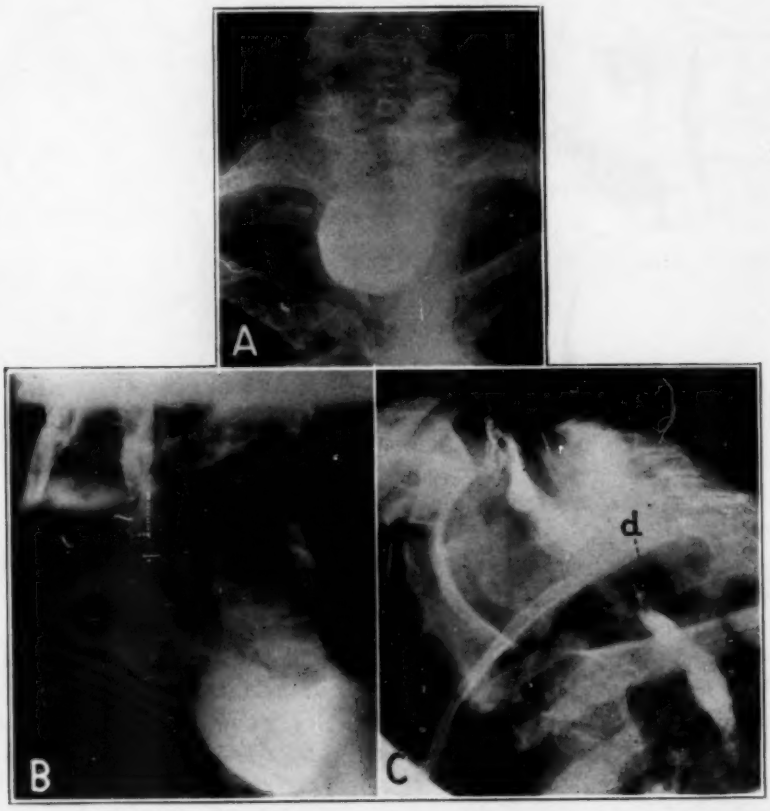

Fig. 3 (case 3).—*A* and *B*, roentgenograms taken before operation. *C*, roentgenogram taken ten days after operation; *d*, the former site of the diverticulum.

cautery. The proximal hemostat, which seals the wall of the esophagus, remains in place with its handles exteriorized through the wound. By the time the hemostat sloughs off in from six to eight days, walling off of the wound has occurred.

This operation with minor variations has been used by me in 5 cases during the past two years. It is illustrated in figure 1. Because an excellent result was obtained in each instance, this experience is reported as evidence in addition to that reported by Maxeiner and others that the operation is as sound in practice as it is in principle.

The minor variations in technic consisted of placing the occluding hemostat with the handles directed upward and of covering all surfaces of the wound with sulfanilamide powder. In each instance a Levine tube was threaded through a nostril into the stomach immediately after

Data on Five Cases of Esophageal Diverticulum

Case	Age of Patient, Year	Sex of Patient	Duration of Dysphagia	Ingestion of Fluids Only	Loss of Weight, Lbs.	Hemostat Off Days	Duration of Fistula, Days	Post-operative Days in Hospital
1	64	M	1.5 yr.	6 weeks	18 (8.2 Kg.)	7	3	9
2	67	F	7 yr.	1 yr.	30 (13.6 Kg.)	7	2	10
3	76	M	6 mo.	2 mo.	15 (6.8 Kg.)	6	4	12
4	52	M	3 yr.	.....	None	6	3 (recurred)	8
5	51	M	6 yr.	.....	25 (11.3 Kg.)	7	3	8

operation, and high caloric liquids well supplied with proteins and fortified with large doses of vitamin B complex and vitamin C were administered in sufficient quantity to maintain complete fluid balance and to assure normal caloric requirements. This method of feeding was used for five or more days, when food could be swallowed without much difficulty. In 3 cases moderate degrees of malnutrition had developed; the patients were given dextrose and vitamin therapy parenterally for a few days before operation.

Two patients were discharged from the hospital in eight days after operation: 1 was discharged in nine; 1, in ten; and 1 in twelve. In only 1 case did an esophageal fistula persist longer than four days after the hemostat came off and at no time in all cases was there more than a slight seepage. In the 1 case the fistula, which presumably had closed within three days, reopened a few days later through the wound, which had completely healed during the interval. After five days it permanently closed.

Brief reports of cases are given in the table.

1418 Medical Arts Building.

INFLUENCE OF VITAMIN B COMPLEX DEFICIENCY AND PARTIAL STARVATION ON WOUND HEALING

EXPERIMENTAL RESEARCH WITH RATS

JANET C. HOLDEN, M.D.
AND
GEORGE CRILE JR., M.D.
CLEVELAND

The literature on the effect of the vitamin B complex on wound healing is confined to observations on surface healing and is summarized by Arey [1] in his article on wound healing. Saitta [2] found that a deficiency in the vitamin B complex resulted in diminished power of cicatrization in wounds of the skin, the subcutaneous tissue and the muscles. Oral administration of extract of cereals prevented these changes, and direct treatment of the wounds with the vitamin B complex produced normal activation of the cellular repair. Lauber [3] emphasized the unreliability of results obtained with the vitamin B complex and attributed this to a lack of standardization of the exact amounts of the vitamin in vitamin B-rich diets. He found no difference in wound healing between control animals and animals fed with yeast. Larcher [4] found that wounds in pigeons suffering from a deficiency of the vitamin B complex healed with equal rapidity or faster than similar wounds in a control series. Padula [5] found that the local application of vitamin B complex to a wound slowed the rate of healing in normal animals but increased it in animals maintained on a diet low in vitamins. Healing was found to be still faster when the deficient animals were subsequently given a normal diet to which vitamins were added. Howes, Briggs and Harvey [6] found that in partially starved adult rats the curve of fibroplasia was not markedly changed from normal.

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1. Arey, L. B.: Physiol. Rev. **16**:327-406 (July) 1936.
2. Saitta, S.: Scritti biol. **5**:273-283, 1930.
3. Lauber, H. J.: Beitr. z. klin. Chir. **158**:293-302, 1934.
4. Larcher, A.: Arch. di fisiol. **25**:348-360 (July-Sept.) 1927.
5. Padula, A.: Arch. ital. di chir. **42**:627, 1936; abstracted, Internat. Abstr. Surg. **63**:288, 1936; in Surg., Gynec. & Obst., September 1936.
6. Howes, E. L.; Briggs, H.; Shea, R., and Harvey, S. C.: Effect of Complete and Partial Starvation on Rate of Fibroplasia in Healing Wound, Arch. Surg. **27**:846 (Nov.) 1933.

EXPERIMENTS TO DETERMINE EFFECT OF A DEFICIENCY OF THE VITAMIN B COMPLEX ON WOUND HEALING

A series of experiments were carried out on the albino male rat to determine the effect of vitamin B complex deficiency on wound healing.

Two groups of rats were observed; there were 14 rats in each group.

Group 1—Normal adult controls

Group 2—Rats maintained on a diet deficient in the vitamin B complex

Group 1 was given the following normal diet:

Casein	400 Gm.
Osborne-Mendel salt mixture	80 Gm.
Corn starch	1,320 Gm.
Cottonseed oil	160 Gm.
Cod liver oil	40 Gm.
Yeast	200 Gm.

Group 2 was given the following diet deficient in vitamin B complex:

Purified casein (heated in an oven at 212 F. for forty-eight hours)	400 Gm.
Osborne-Mendel salt mixture	80 Gm.
Corn starch	1,320 Gm.
Cottonseed oil	160 Gm.
Cod liver oil	40 Gm.

Wound healing in the rats was tested by the method of Harvey.[7] An experimental wound 2 cm. long was placed in the midline of the wall of the abdomen and was closed with a through and through running suture of black silk. The operation was performed with aseptic technic. The suture was removed one week after operation. The tensile strength of the wound was tested on the eighth and the tenth postoperative day by inflating the abdomen with air injected into the peritoneal cavity through a lumbar puncture needle. The breaking point of the incision was measured on a mercury sphygmomanometer. The appearance of the wound and the presence or absence of peritonitis were noted. The manometer measured only to 300 mm. of mercury, and figures above this level are recorded as 300.

In each group 6 animals were killed on the eighth postoperative day (subdivision A), and 6 animals were killed on the tenth postoperative day (subdivision B).

The seventh animal in each division was used for histologic studies. Each group of rats was kept on its respective diet an equivalent length of time. The rats were weighed once a week. When the vitamin-deficient rats had lost about 30 per cent of their original weight, they were subjected to operation.

The average tensile strength of the wounds was lower in the vitamin B-deficient rats tested on the eighth postoperative day than in the controls, but by the tenth postoperative day the average tensile strength of the wounds of the vitamin B-deficient group was actually a little higher than that of the control group. In this experiment, however, the average tensile strength is perhaps not so significant a figure as the number of rats whose wounds withstood a pressure of 300 mm. of mercury. Since the manometer registered nothing higher than 300, a single low figure, such as the 120 recorded for rat 1 of group 1 *A*, tends to make a consid-

7. Harvey, S. C.: The Velocity of the Growth of Fibroblasts in the Healing Wound, Arch. Surg. **18**:1227 (April) 1929.

erable difference in the average tensile strength. Actually the wounds of 7 rats in the vitamin B-deficient group and of 7 rats in the control group withstood a pressure of 300 mm. of mercury, indicating that a deficiency of vitamin B complex

TABLE 1.—*Gain or Loss of Body Weight and Tensile Strength of Wound in Normal Adult Control Animals*

Rat	Percentage of Total Body Weight Gained or Lost During Experiment	Tensile Strength of Wound, Mm. of Mercury
Group 1A.—Killed on the Eighth Postoperative Day		
1	− 1	300
2	+ 1	300
3	− 1	240
4	+ 1	300
5	− 2	260
6	− 2	300
Group 1B.—Killed on the Tenth Postoperative Day		
1	+ 2	300
2	− 3	270
3	+ 5	300
4	− 1	270
5	+ 4	300
6	+ 4	270
Average	+ 1	285

TABLE 2.—*Gain or Loss of Body Weight and Tensile Strength of Wound in Adult Rats Given a Diet Deficient in Vitamin B*

Rat	Percentage of Total Body Weight Gained or Lost During Experiment	Tensile Strength of Wound, Mm. of Mercury
Group 2A.—Killed on the Eighth Postoperative Day		
1	−36	120
2	−46	200
3	−19	300
4	−35	220
5	−27	300
6	−34	210
Average	−33	225
Group 2A.—Killed on the Tenth Postoperative Day		
1	−41	300
2	−23	300
3	−43	280
4	−41	300
5	−13	300
6	−42	300
Average	−34	296

has little if any effect on wound healing if the results from the animals tested on the eighth day and on the tenth day are averaged together as though for a single group.

It is interesting to note that the number of wounds attaining strength enough to resist a pressure of 300 mm. of mercury was less and that the average breaking

point of the wounds was at a lower pressure in the rats on a vitamin B-deficient diet killed on the eighth postoperative day than in the control group. These figures, however, are not sufficiently striking to be outside the range of experimental error.

EXPERIMENTS TO DETERMINE EFFECT OF A LOW CALORIC DIET ON WOUND HEALING

Although we did not believe that it would be fair to conclude from the figures just given that a deficiency of vitamin B retarded the early stages of wound healing, we were unable to exclude this possibility and therefore undertook the study of a second control group. The animals in this group were given a low caloric diet designed to effect a loss of weight equivalent to the weight lost by the vitamin B-deficient rats in group 2. This diet consisted of one half of the diet used in the normal controls (group 1) and contained adequate vitamins to prevent deficiency.

TABLE 3.—*Gain or Loss of Body Weight and Tensile Strength of Wound in Adult Rats Given a Low Caloric Diet*

Rat	Percentage of Total Body Weight Gained or Lost During Experiment	Tensile Strength of Wound, Mm. of Mercury
Group 3A.—Killed on the Eighth Postoperative Day		
1	—26	300
2	—48	300
3	—31	240
4	—37	180
5	—32	200
6	—37	270
Average	—35	248
Group 3B.—Killed on the Tenth Postoperative Day		
1	—32	180
2	—34	200
3	—43	270
4	—31	300
5	—33	300
6	—43	170
Average	—36	236

In this group the wounds were less solidly healed on both the eighth and the tenth postoperative day than in the control group. Moreover, the number of wounds which resisted a pressure of 300 in the rats killed on the eighth postoperative day was exactly equal to that in the vitamin B-deficient group on the same day. These findings indicate that if a deficiency of vitamin B complex has any deleterious effect on wound healing, this effect is probably associated with the loss of weight which accompanies the deficiency rather than the result of the vitamin B deficiency itself. In short, loss of weight, whether due to vitamin deficiency or to deficiency in caloric intake, appears to cause some delay in wound healing.

COMMENT

Abdominal wounds in normal adult control rats were healed with equal strength on the eighth and the tenth postoperative day. The rats neither gained nor lost weight during the experiment.

Rats maintained on a diet deficient in vitamin B complex lost 33 to 34 per cent of their original weight, and on the eighth postoperative day their wounds were not as well healed as those of the controls. On the tenth postoperative day, however, these wounds were healed as solidly as the wounds of the animals in the control group.

Rats maintained on a low caloric diet lost 35 to 36 per cent of their original weight, and on both the eighth and the tenth postoperative day their wounds had failed to heal as well as those of the controls.

On the eighth postoperative day the strength of the wounds was practically the same in the vitamin B-deficient group and in the group maintained on a low caloric diet.

There seemed to be no correlation between the appearance of the wound and its tensile strength. No peritonitis was noted in any of the rats. Histologic examination of the wounds showed only the presence or the absence of surface infection and failed to reveal any apparent cause for the difference in tensile strength of the wounds in the different groups.

CONCLUSIONS

In adult albino rats a deficiency in vitamin B complex has little effect on wound healing.

The slight diminution in the tensile strength of the wounds in vitamin B-deficient rats killed on the eighth postoperative day is probably explained by factors associated with their loss of weight rather than by any specific effect of the vitamin deficiency.

Wound healing in the albino rat appears to be more closely related to changes in body weight than to deficiencies of the vitamin B complex.

STIMULATION OF THE CELIAC PLEXUS IN THE DOG

II. FACTORS INFLUENCING CARDIOVASCULAR AND RESPIRATORY RESPONSES

S. J. MARTIN, M.D.

C. L. BURSTEIN, M.D.

AND

E. A. ROVENSTINE, M.D.

NEW YORK

In a previous report,[1] it was shown that mechanical and faradic stimulation of the celiac plexus in the dog is usually followed by a predominant response characterized by a rise in the mean arterial and venous pressures, a decrease in the pulse pressure, sinus tachycardia and apnea followed by polypnea or a gradual return to normal respiration. It was pointed out also that certain factors, such as the strength of the stimulation applied and the anesthetic drugs employed, influence the character of this response. Stimulation of the sympathetic system may play an important role. An attempt is made in the present investigation to determine (1) the role of other factors, such as premedication, depth of anesthesia and curarization, on the appearance of the predominant response to stimulation of the celiac plexus in the dog and (2) the nature of the mechanism involved.

PROCEDURE

In a group of 19 adult dogs under anesthesia induced with ether, cyclopropane or chloralosane,[2] the celiac plexus, the left splanchnic and right vagal nerves were exposed and prepared for mechanical and faradic stimulation; the strength of the stimuli was kept uniform. Other procedures were completed for recording the arterial blood pressure and respiratory changes.[1]

Circulatory and respiratory changes from celiac plexus stimulation were noted as follows: (1) before premedication; (2) one hour after the subcutaneous administration of morphine sulfate (5 mg. per kilogram of body weight) or (3) atropine sulfate (0.05 to 0.1 mg. per kilogram) or (4) both drugs. The dogs

From the Division of Surgery, Department of Anesthesia, New York University College of Medicine.

1. Martin, S. J.; Burstein, C. L., and Rovenstine, E. A.: Stimulation of the Celiac Plexus in the Dog: I. Cardiovascular and Respiratory Effects, Arch. Surg. 44:943 (May) 1942.

2. Chloralosane is a preparation of chloralose (a compound of chloral hydrate and dextrose) which has been purified of parochloralose and other impurities.

used for these observations were subsequently employed in the studies hereinafter noted.

Six dogs were anesthetized with ether or cyclopropane after premedication with morphine and atropine. The depth of anesthesia was varied from light (plane 1) and medium (plane 2) to deep (plane 4) levels to determine the significance of this factor on the predominant response to stimulation of the celiac plexus.

The influence on the response to stimulation of the celiac plexus of a purified curare preparation [3] (0.07 to 0.5 mg. per kilogram) given intravenously or of a 4 per cent solution of procaine hydrochloride topically applied was investigated in 6 animals.

Special surgical procedures were carried out on 7 dogs; these consisted of (1) bilateral lumboadrenal vein ligation, (2) a spinal block with procaine hydrochloride (150 mg.) or pontocaine hydrochloride (20 mg.) to the level of the second to the fourth thoracic segment and (3) a spinal cord section at the level of the second cervical vertebra.

In all experiments, control records of the mean arterial and pulse pressures and of the rate and amplitude of respirations were compared with those taken during and after the various procedures already cited.

RESULTS

Modifying Factors.—(*a*) Premedication: A series of fourteen observations revealed that mechanical or faradic stimulation of the celiac plexus in etherized dogs (plane 2) when there had been no preanesthetic medication or when morphine sulfate had been given usually elicited either no change in the cardiovascular or respiratory systems or occasionally a slight rise in the mean arterial blood pressure (10 to 30 mm. of mercury), a small decrease in the pulse pressure (2 to 10 mm. of mercury) and short apnea. However, when stimulation followed the administration of atropine sulfate, alone or with morphine, the characteristic predominant responses in circulation and respiration were noted (figs. 1 and 2).

(*b*) Curare: The intravenous administration to 4 etherized dogs of a purified curare preparation in amounts adequate to produce intercostal paralysis did not prevent the rise in the blood pressure previously noted following mechanical and faradic stimulation of the celiac plexus or the proximal end of the cut left splanchnic nerve. However, a marked diminution in the magnitude of the response was noted. The rise in the mean arterial blood pressure averaged 10 mm. of mercury; a slight transient fall in the blood pressure occasionally preceded the rise. Further, the decrease in the pulse pressure was negligible. Stimulation of the abdominal vagus nerve was without effect.

Mechanism Involved.—(*a*) Procaine Hydrochloride Topically Applied: Ten minutes after the topical application of 4 cc. of a 4 per

3. Intocostrin, 1 cc. containing a potency equivalent to 10 mg. of curare, was supplied by E. R. Squibb & Sons.

cent solution of procaine hydrochloride to the celiac plexus, tension on the viscera of the upper part of the abdomen or mechanical and faradic stimulation of the celiac plexus failed to produce any cardiovascular and respiratory change in ten observations of 2 etherized dogs. The effect of the procaine hydrochloride lasted not less than seventy minutes. It thus seems that all reflex pathways from the viscera of the upper part of the abdomen pass through the celiac plexus and that they can be blocked by the application of procaine hydrochloride to that region.

(*b*) Bilateral Lumboadrenal Vein Ligation: Bilateral lumboadrenal vein ligation was performed on 2 etherized dogs (plane 2) to determine

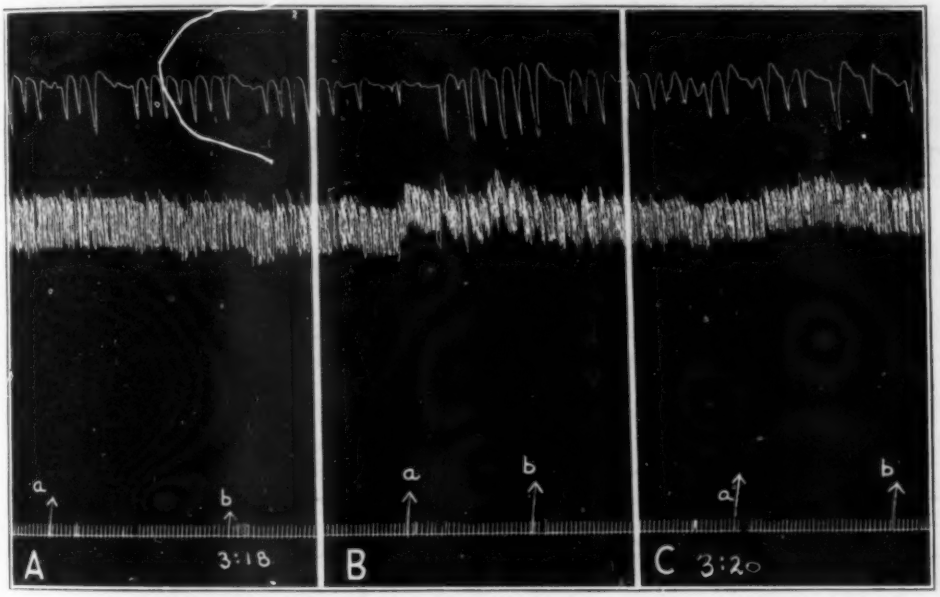

Fig. 1.—Tracings showing the results of faradic stimulation of the celiac plexus (*A*) and the proximal ends of the cut left splanchnic nerve (*B*) and the right abdominal vagus nerve (*C*) of an etherized dog given only morphine premedication. Note the slight or negligible effects on respiration and blood pressure. The upper, middle and lower tracings represent respiration, blood pressure and time in second intervals, respectively; the period of stimulation is noted between arrows.

the influence of the secretion of epinephrine on the predominant cardiovascular and respiratory response following stimulation of the celiac plexus. It was found that such a procedure had little or no significant effect on the appearance of the usual circulatory and respiratory response following mechanical or faradic stimulation of the plexus. In 3 instances the arterial pressure increase was of shorter duration and not as great as the control levels taken prior to ligation of the veins.

(*c*) Spinal Anesthesia and Section of the Spinal Cord: In 3 dogs under anesthesia induced with chloralosane (80 to 90 mg. per kilogram), procaine hydrochloride or pontocaine hydrochloride was injected subdurally to produce anesthesia to the level of the second to the fourth thoracic nerve segments. Intercostal muscles were paralyzed, and only diaphragmatic excursions maintained respiration. It was noted consistently that the cardiovascular and respiratory changes noted in control records after mechanical and faradic stimulation of the celiac plexus or on visceral tension were absent when such stimulation was employed during spinal anesthesia.

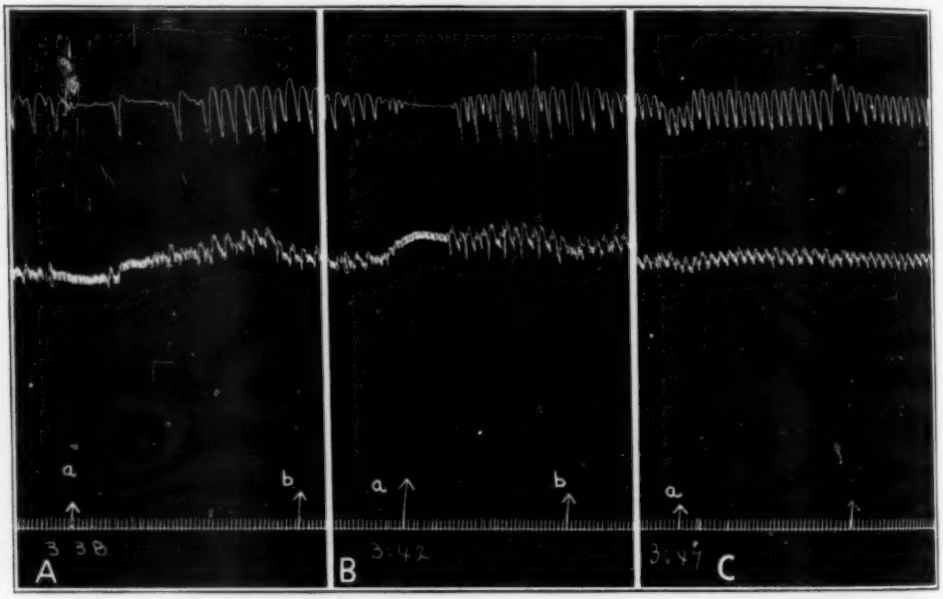

Fig. 2.—Tracings of a dog given the same treatment as the dog whose tracings are shown in figure 1 except that atropine sulfate was given one hour before stimulation. Note the apnea, the rise in the mean arterial blood pressure and the decrease in the pulse pressure after faradic stimulation of the celiac plexus (*A*) and the splanchnic nerve (*B*). No change followed stimulation of the abdominal vagus nerve (*C*).

The spinal cord was sectioned at the level of the second cervical vertebra in 2 dogs, and the respirations were artificially controlled. The afferent path from the celiac plexus was thus destroyed, while the efferent path from this region was left intact. Neither mechanical nor faradic stimulation of the celiac plexus nor visceral tension produced any change simulating the predominant cardiovascular and respiratory effects noted prior to section of the cord.

COMMENT

It was reported that stimulation of the celiac plexus in the dog resulted in a predominant cardiovascular and respiratory pattern. The same study suggested that certain factors, other than the type and the strength of the stimuli, may play an important role.[1] The data in the present investigation illustrate the significance of premedication with atropine in facilitating the appearance of the rise in the arterial pressure, the decrease in the pulse pressure and, to a less extent, the onset of apnea following stimulation of the celiac plexus. The parasympatholytic action of atropine apparently imbalances autonomic equilibrium and enhances sympathetic influences. Such supposed imbalance has been accepted as the rational basis of premedication with physostigmine salicylate to prevent deleterious responses to visceral stimulation.[4]

The depth of anesthesia similarly is of great importance in facilitating the response to stimulation of the celiac plexus. Changes in the levels of anesthesia did not reverse the nature of the cardiovascular and respiratory pattern but merely changed the magnitude of the pattern. The depth of anesthesia is only to be emphasized as another factor to reckon with in seeking uniform results in stimulation of the celiac plexus.

Curarization to the point of intercostal paralysis in anesthetized dogs did not eliminate the rise in the blood pressure that follows stimulation of the celiac plexus. Hence, the effect that changes in respiration or the elimination of efferent intercostal stimuli may have on the predominant response after celiac plexus or visceral stimulation appears to be ruled out. Changes in respiratory activity, therefore, are not primarily responsible for the circulatory effects; however, they can augment them. It must be emphasized that curarization up to the point of intercostal paralysis differs from plane 4 anesthesia in that the central nervous system is not depressed in the former procedure and hence stimulation of the celiac plexus can elicit reflex changes.

The mechanism involved in the cardiovascular and respiratory changes following stimulation of the celiac plexus appears to depend essentially on the integrity of the sympathetic nervous system. This was suggested previously when it was noted that such responses were not affected by severing the abdominal vagus nerve but were markedly diminished after stimulation of the celiac plexus following section of the left splanchnic nerve. Further studies substantiated this contention. Thus, (1) topical application to the celiac plexus of procaine hydrochloride to block all reflex stimuli prevented changes in circulation and respiration when the plexus or the viscera of the upper part of the abdomen were stimulated; (2) blocking of the entire path by high spinal

4. Garrelon, L.; Pascalis, G., and Thuillant, L.: Presse méd. **38**:1365, 1930.

anesthesia similarly resulted in no changes in circulation or respiration following stimulation of the celiac plexus, and (3) section of the spinal cord, whereby the afferent reflex path was eliminated and the peripheral efferent path left intact from the celiac plexus, likewise produced no circulatory or respiratory changes on plexus stimulation. It is particularly significant that the parasympathetic path from the region of the viscera of the upper part of the abdomen or the celiac plexus was not disturbed by spinal anesthesia or section of the spinal cord. It may be concluded, therefore, that responses to stimulation of the celiac plexus or stimulation of the viscera of the upper part of the abdomen depend essentially on an intact sympathetic pathway. The experiments concerned with lumboadrenal vein ligation demonstrate the fact that the secretion of epinephrine is not necessary for the appearance of the responses to stimulation of the celiac plexus. The mechanism, while sympathetic in origin, is fundamentally neural and not hormonal.

SUMMARY AND CONCLUSIONS

Mechanical and faradic stimulation of the celiac plexus of dogs under anesthesia induced with ether or cyclopropane is followed by a rise in the mean arterial pressure, a decrease in the pulse pressure, sinus tachycardia and apnea. The appearance of such predominant changes is markedly facilitated by the use of atropine sulfate for preanesthetic medication. Morphine as a premedicant exerts no such influence.

The cardiovascular and respiratory effects following celiac plexus stimulation become magnified during light (plane 1) anesthesia and may be completely eliminated during deep (plane 4) anesthesia.

Curarization of etherized dogs up to the point of intercostal paralysis diminishes the response to stimulation of the celiac plexus but does not eliminate it.

Topical application of solution of procaine hydrochloride to the celiac plexus, spinal anesthesia or high section of the spinal cord eliminates circulatory and respiratory changes following faradic stimulation of the celiac plexus or application of tension to the viscera of the upper part of the abdomen.

The characteristic response to stimulation of the celiac plexus is dependent on afferent reflex stimulation of the sympathetic nervous system. It is augmented by respiratory changes or by any secretion of epinephrine that may result from such stimulation.

HEMOSTATIC EFFECT OF OXALIC ACID

CLINICAL AND EXPERIMENTAL RESULTS, WITH A REVIEW OF THE LITERATURE

ALEXANDER W. BLAIN, M.D.
Professor of Clinical Surgery, Wayne University College of Medicine
AND
KENNETH N. CAMPBELL, M.D.
DETROIT

Despite normal coagulation and ordinarily careful hemostasis, sufficient blood may be lost during and following operative procedures, chiefly from capillary oozing, to produce such complications as serum collection, wound infection and disruption and even postoperative shock. Delayed convalescence often results. If during or immediately after operation, a drug could safely be administered to the patient which would definitely hasten coagulation, it would constitute a valuable adjunct to mechanical hemostasis and an important advancement in operative surgery. This is true when the coagulation time is normal and more particularly so when it is delayed.

Several commercial products claimed to accelerate blood coagulation have been available for some time. Aggeler and Lucia,[1] in a recent biologic assay of seventeen of these products, found that nine were practically inactive in vitro. The only products found to be significantly active were those suitable for local or oral use. It can readily be deduced, therefore, that before the hemostatic effect of any substance is generally accepted, it must withstand severe clinical and experimental investigation.

In 1939, Steinberg and Brown[2] found that extracts prepared from certain plants containing oxalic acid accelerated the rate of blood coagulation. On employing pure solutions of oxalic acid, they found that as little as 2 mg. when administered to rabbits was sufficient to reduce the clotting time as much as 50 per cent within fifteen minutes and that it remained reduced for one hour or more. Optimal effects were obtained with 10 mg. of oxalic acid (table 1).

From the Department of Surgery, Alexander Blain Hospital.

1. Aggeler, P. M., and Lucia, S. P.: The Potency of Blood Coagulating Substances: A Biologic Assay, Am. J. M. Sc. **199**:181, 1940.

2. Steinberg, A., and Brown, W. R.: A New Concept Regarding the Mechanism of Clotting and the Control of Hemorrhage, Am. J. Physiol. **126**:638, 1939.

Steinberg and Brown pointed out also that the administration of an excessive amount of oxalic acid to animals causes calcium depletion, a prolongation of clotting time and finally death, while the administration of small amounts reduces the coagulation time even in hirudinized animals. They concluded that oxalic acid is therefore antagonistic to antithrombin and emphasized that in vivo and in vitro experiments are not comparable, as has been demonstrated many times. This statement was adequately supported by the work of Hammarsten,[3] Horne,[4] Vines[5] and Scott and associates.[6]

The hemostatic extracts investigated by Steinberg and Brown[2] were subsequently used in several thousand clinical cases with satisfactory results. Schumann[7] found that plant extracts containing oxalic acid were effective in the treatment of postpartum hemorrhage and uterine bleeding. Later he treated patients with oxalic acid solution and obtained uniformly good results. Segal[8] treated a variety of patients exhibiting hemorrhage or hemorrhagic dyscrasia with both plant extracts and oxalic acid and obtained fairly rapid control of the bleeding. Milliken[9] reported the use of a plant extract in clearing the field of operation for transurethral prostatic resection and felt that it greatly facilitated the operative procedure. Recently, Jackson[10] discussed the use of plant extracts and an oil solution of the ethyl esters of dibasic acids in the treatment of gastrointestinal hemorrhage and noted a satisfactory response. Steinberg, in a personal communication, reported satisfactory results in 160 patients exhibiting bleeding tendencies. Included in this series were cases of hemophilia, jaundice, purpura, leukemia and uterine bleeding. A subsequent article by Steinberg and co-workers[11] cited the results obtained in several hundred cases in which the patients were carefully followed.

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3. Hammarsten, O.: The Clotting of Fibrin, Arch. f. d. ges. Physiol. **14**:211, 1877.

4. Horne, R. M.: The Action of Strontium, Barium and Calcium Salts in Preventing Coagulation of Blood, J. Physiol. **19**:356, 1896.

5. Vines, H. W. C.: The Role of Calcium in Blood Coagulation, J. Physiol. **55**:86, 1921.

6. (*a*) Scott, F. H., and Chamberlain, C.: Calcium and Blood Coagulation, Am. J. Physiol. **91**:27, 1930. (*b*) Scott, F. H., and Loucks, N. M.: Calcium and Blood Coagulation, Proc. Soc. Exper. Biol. & Med. **31**:1054, 1934.

7. Schumann, E. A.: Newer Concepts of Blood Coagulation and the Control of Hemorrhage, Am. J. Obst. & Gynec. **38**:1002, 1939.

8. Segal, H. I.: Personal communication to the authors.

9. Milliken, L. F.: The Use of a New Blood Coagulant in Transurethral Prostatic Resection, J. Urol. **42**:75, 1939.

10. Jackson, A. S.: Editor's Comments, Jackson Clin. Bull. **2**:3, 1940.

11. Steinberg, A.; Segal, H. I., and Parris, H. M.: Role of Oxalic Acid and Certain Related Dicarboxylic Acids in Treatment and Control of Hemorrhage, Ann. Otol., Rhin. & Laryng. **49**:1008, 1940.

The suggestion that oxalic acid promoted coagulation was rather startling and seemed paradoxic, since the oxalates are well known anticoagulants in vitro. However, in the past decade approximately one hundred and seventy-five articles dealing with the pharmacology and metabolism of oxalic acid have appeared in the medical literature. One hundred and forty-five of these articles appeared in Italian, German, Japanese and French periodicals; only a few were published in American or English journals.

Suzuki's [12] method for the quantitative determination of oxalic acid in blood was modified by Steinberg, and by this method normal values for human beings were established between 5.5 and 7.5 mg. per hundred cubic centimeters of blood and for rabbits between 2.5 and 6.0 mg. Other investigators [13] have placed the normal blood level of oxalic acid in human beings between 2 and 8 mg. per hundred cubic centimeters of blood. These values have been confirmed by us, using the Steinberg modification.

METABOLISM OF OXALIC ACID

It is generally believed that oxalic acid is dangerously poisonous. MacKenzie and McCollum [14] stated that the smallest recorded lethal dose of oxalic acid for man, administered orally, is 4 Gm. and quoted Koch to the effect that 3 Gm. of oxalic acid, given by stomach tube, is the lethal dose for cats and 1.8 Gm., for rabbits. About one eighth of these doses were lethal when injected parenterally. Many commonly administered drugs are much more highly toxic than oxalic acid.

In an attempt to produce oxalate nephritis experimentally in dogs, Arnott and Kellar [15] experienced some difficulty, even with repeated doses of as high as 100 mg. of sodium oxalate. Even with such large doses, histologic glomerular lesions could not be produced, although albuminuria was noted. Likewise no degenerative changes in the liver were produced.

That oxalemia is an accompaniment of any form of hyperglycemia has been demonstrated on several occasions by many investigators, among

12. Suzuki, S.: Glucose as a Source of Oxalic Acid, Jap. J. M. Sc., II, Biochem. **2**:401, 1934; Adrenalin and Insulin as Factors Causing Variations in Oxalic Acid Level, ibid. **3**:23, 1935.

13. (*a*) Muller, P. B.: Oxalic Acid Metabolism in Man and Animals, Schweiz. med. Wchnschr. **68**:964, 1938. (*b*) Schumann.[7] (*c*) Scott and Chamberlain.[6a] (*d*) Segal.[8]

14. MacKenzie, C. J., and McCollum, E. V.: Some Effects of Dietary Oxalate on the Rat, Am. J. Hyg. **25**:1, 1937.

15. Arnott, W. M., and Kellar, R. J.: Hypertension Associated with Experimental Oxalate Nephritis, Brit. J. Exper. Path. **16**:265, 1935.

them Oikawa,[16] Viale,[17] Muller,[13a] Pennetti [18] and de Lucia.[19] De Lucia confined his observations to the elimination of oxalic acid in cases of oxalemia produced by the administration of glucose, either oral or subcutaneous, or by the injection of epinephrine. These experiments were performed on dogs. It appears from the findings presented by the authors mentioned that with hyperglycemia, irrespective of its origin, there exists an excess of oxalic acid and that the amount of oxalic acid corresponds to the degree of hyperglycemia. Possibly the slight reduction in coagulation time associated with the administration of dextrose or epinephrine to human beings is somewhat related to the oxalemia thereby produced. Muller [13a] also showed that in experiments in vitro in which dextrose is added to defibrinated blood, there is an increased production of oxalic acid.

Most of the oxalic acid in the blood is excreted in the urine, a smaller amount through the bile and a small quantity in the saliva. It has been noted by several observers that in cases of hepatic insufficiency, diabetes, pregnancy and various other conditions, there occurs a marked disturbance in oxalic acid metabolism. Since there is experimental evidence that oxalic acid may be an important substance in metabolism, correlative clinical investigation might further the knowledge of the possible role of this substance in the coagulation of blood. At the present time, unfortunately, the physical and chemical changes involved are not well understood.

In tables 1 and 2 as well as in charts 1 and 2 are shown the comparable experimental results obtained by Steinberg and by us. In our experiments a solution of recrystallized oxalic acid with a p_H of 3.5 to 4.8 was given intravenously. The maximum dose given to any single rabbit was 140 mg., and this dose failed to produce histologic changes in the kidneys, the liver, the spleen, the pancreas, the skeletal muscles or the gastrointestinal tract when administered over a three day period. Experimentally, maximum effects occur within thirty minutes after administration. Clinically, a response seems to occur much earlier than this. It is of interest that while the quantities of oxalic acid administered to rabbits varied greatly, a maximum of 50 mg. being administered at

16. Oikawa, S.: Hyperoxalemia Induced by Glucose and Adrenalin, Jap. J. M. Sc., II, Biochem. **4**:41, 1938; Influence of Exercise on Oxalic Acid Excretion, ibid. **4**:17, 1938.

17. Viale, G.: Influence of Insulin on the Metabolism of Oxalic Acid, J. Nutrition **3**:111, 1933; Endocrine Influence on the Metabolism of Oxalic Acid, Rev. sud.-am. de endocrinol. **9**:967, 1926.

18. Pennetti, G.: Oxalemia in Liver Disease, Riforma med. **51**:1358, 1935.

19. de Lucia, P.: The Elimination of Oxalic Acid in Various Forms of Hyperglycemia, Boll. Soc. ital. di biol. sper. **4**:356, 1929.

one time, practically identical results were obtained. This was observed both clinically and experimentally.

We have found that between 20 and 40 mg. is the optimal dose for human beings. The solution can be administered either intravenously or intramuscularly and may be repeated within a short time. It is difficult to explain why similar effects are produced with variable quan-

TABLE 1.—*Experimental Studies of Coagulation Time Made by Steinberg* *

Dose, Mg.	Normal		15 Minutes		30 Minutes		60 Minutes	
	Time	Per Cent	Time	Per Cent	Time	Per Cent	Time	Per Cent
2	153.2	100	132.4	86.4	102.0	66.5	93.4	60.9
4	208.6	100	64.0	30.6	42.0	20.1	55.0	26.3
5	125.8	100	62.0	50.8	34.0	27.0	80.0	63.5
10	112.4	100	42.8	38.0	34.4	30.6	52.9	47.0
50	242.2	100	171.4	70.7	65.0	26.8	167.0	68.9
	Average.....			55.3		34		53.3

* This table gives the results obtained by Steinberg from rabbits. The figures represent the time in seconds; percentages given are of the normal values. Note that the greatest reduction in coagulation time occurred in thirty minutes in practically all cases.

TABLE 2.—*Experimental Studies of Coagulation Time Made by Blain and Campbell* *

Dose, Mg.	Normal		15 Minutes		60 Minutes	
	Time	Per Cent	Time	Per Cent	Time	Per Cent
2	140.2	100	60.4	43.0	90.6	64.6
4	218.8	100	80.6	36.8	110.8	50.6
5	200.2	100	99.2	49.5	102.8	51.3
10	186.6	100	90.6	48.7	98.8	52.4
Average.....				44.5		54.7

* The figures represent the time in seconds; the normal time is given as the average of ten determinations. Oxalic acid solution (recrystallized, p_H 3.5 to 4.8), original acidity reduced with sodium hydroxide, was given by intravenous administration in all cases. Five rabbits were used in this series. Single trials of each dosage were given at daily intervals to each rabbit. The maximum amount given any single animal—140 mg.—failed to produce microscopic lesions in the kidneys, the liver, the spleen, the pancreas, the muscles or the gastrointestinal tract when administered over a three day period. Note that the results closely parallel those of Steinberg.

tities of oxalic acid. Oxalic acid apparently has little or no effect on prothrombin time (table 3).

In the first 100 cases in this series, oxalic acid solution in amounts varying between 20 and 60 mg. was administered more or less routinely to patients before or during operation, and the patients were carefully observed for any deleterious effects. None were detected. The succeeding cases were selected because in them excessive and troublesome oozing was encountered during operation and oxalic acid solution was administered after the operation was begun. A wide variety of surgical

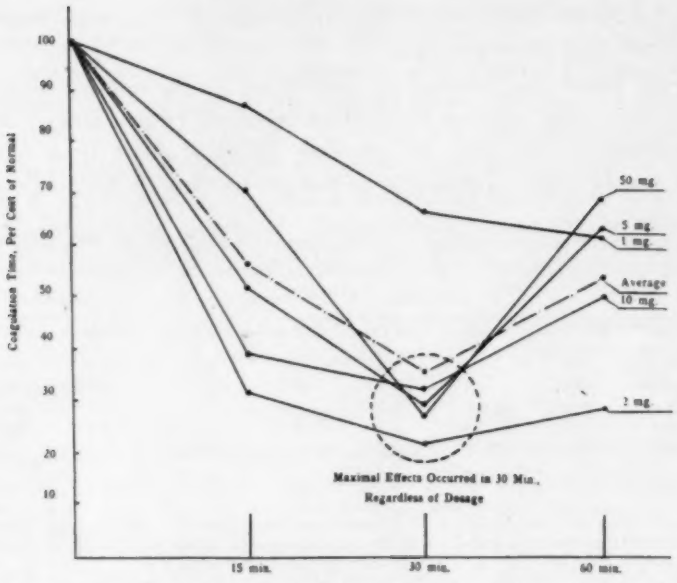

Chart 1.—Graphic analysis of Steinberg's experimental results given in table 1.

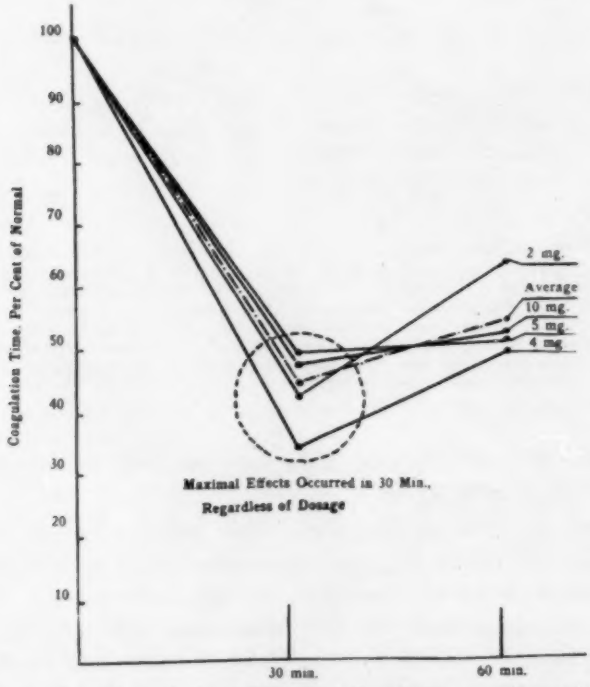

Chart 2.—Graphic analysis of Blain and Campbell's experimental results given in table 2.

procedures was included, and observations were made in the departments of urology and otolaryngology of the hospital as well as in the department of general surgery. In every case the result was recorded as satisfactory or excellent, and in most cases one administration of oxalic acid solution was sufficient to control oozing. Good clot formation occurred, the operative field was made much drier, and secondary hemorrhage was believed to have been prevented. In thyroidectomy, vaginal hysterectomy and cholecystectomy, we have found the practical advantages of this hemostatic agent particularly outstanding. The coagulation time,

TABLE 3.—*Determination of Prothrombin Time Before and After the Administration of Oxalic Acid in Consecutive Cases in Which Operation Was Performed* *

Operative Procedure	Prothrombin Time Before Operation (Sec.)	Control Time (Sec.)	Oxalic Acid Administered (Mg.)	Prothrombin Time After Operation (Sec.)	Control Time (Sec.)	Comment
Thyroidectomy.....	18	13	20	16	14	Slight reduction
Cholecystectomy and appendectomy	13	13	40	13	14	No change
Thyroidectomy.....	18	13	20	15	15	Slight reduction
Hemorrhoidectomy....	17	13	20	18	15	No change; minimal increase
Thyroidectomy.....	13	13	20	15	18	Slight increase
Vaginal hysterectomy	15	15	40	14	12	Slight reduction
Thyroidectomy.....	17	15	20	16	12	Slight reduction
Hemorrhoidectomy....	16	15	20	16	12	No change
Herniorrhaphy.....	20	15	20	17	15	Slight reduction
Herniorrhaphy.....	17	12	20	14	14	Slight reduction
Hemorrhoidectomy....	18	12	20	17	14	Slight reduction
Hysterectomy.....	15	12	40	14	14	Slight reduction
Amputation cervix....	12	12	20	13	14	Minimal increase
Amputation cervix....	14	12	20	13	14	Slight reduction
Herniorrhaphy.....	16	12	20	16	14	No change

* Prothrombin values were determined by the Quick method. Oxalic acid was administered during operation.

determined by the method of Lee and White, was decreased in every case, confirming the experimental results to which we have already referred.

The control of bleeding in the operative field by methods other than ligation and electrodesiccation is at present difficult. At times an excessive amount of suture material is introduced into an operative wound, particularly in the thyroid area, in order to get a dry wound, and the use of dextrose solution and the application of hot compresses are time consuming and traumatize tissues. It is in those troublesome cases that after all of the bleeders have been ligated, but capillary oozing continues to a marked degree, the effect of oxalic acid solution has been most dramatic clinically. Postoperative sequelae have been favorably

influenced, particularly wound infection. In our opinion, wound infection occurs not entirely from the introduction of micro-organisms but as well from the collection of blood or serum in wounds. Excessive oozing cannot always be anticipated before operation, and because the drug in the doses given is entirely harmless, we pursue the practice of administering oxalic acid routinely in certain types of major operation. Patients with jaundice and deficiency of vitamin K have not been included in this discussion.

METHOD OF PREPARATION

Since oxalic acid in aqueous solution is unstable at high temperatures, overheating must be avoided in its preparation, and pressure sterilization cannot be utilized. A saturated solution is first prepared by dissolving chemically pure oxalic acid in sterile distilled water at 60 C. This solution is cooled in a refrigerator to 5 C., and the precipitated oxalic acid is filtered. Strict aseptic precautions should be observed in each step. Ten grams of dried recrystallized oxalic acid is then dissolved in 800 cc. of sterile distilled water. One hundred and forty cubic centimeters of normal sodium hydroxide is then added, sufficient distilled water being finally added to bring the volume to 1 liter. The hydrogen ion concentration of this solution then varies between 3.5 and 4.3. The solution is next filtered through a Berkefeld filter, and the finished product is placed in sterile amber ampules or vaccine bottles of a capacity not greater than 5 cc. These ampules or bottles are stored in the refrigerator. A small amount of phenol may be added as a preservative if desired. One cubic centimeter of the finished product contains 10 mg. of oxalic acid.

CLINICAL OBSERVATIONS

In the administration of oxalic acid to 440 operative patients, on whom nearly all major operative procedures were performed, the following observations were made:

1. Either immediate cessation of hemorrhage or a noticeable decrease in oozing occurred in practically all cases.

2. There was a definite measurable reduction in coagulation time.

3. There was no appreciable decrease in prothrombin time.

4. The best clinical results were obtained in those cases in which a large oozing surface constituted the source of hemorrhage.

5. There was no clinically demonstrable renal damage following the administration of oxalic acid.

6. In no case did thrombophlebitis develop after the use of this drug, nor were there any untoward clinical reactions.

7. There was an apparent decrease in the amount of serum collection in the incisional wound.

8. The administration of oxalic acid effectively controlled bleeding associated with carcinoma.

SUMMARY

A sterile aqueous solution of recrystallized oxalic acid has been administered intramuscularly by us in 440 clinical cases to control bleeding incident to surgical procedures and has been found to be a satisfactory hemostatic agent in all circumstances.

It is now used routinely in this hospital as a prophylactic measure against hemorrhage in major surgical procedures in which capillary oozing is anticipated.

The optimal dose for human beings is 20 mg., and this may be repeated if necessary.

Experimental and clinical investigation indicates that the hemostatic effect of oxalic acid is exhibited promptly.

Oxalic acid is a safe, reliable, inexpensive and almost instantly effective hemostatic agent.

2201 Jefferson Avenue, East.

1313 East Ann Street, Ann Arbor, Mich.

REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES
FRANK HINMAN, M.D.
SAN FRANCISCO
ALEXANDER von LICHTENBERG, M.D.
MEXICO, MEXICO
ALEXANDER B. HEPLER, M.D.
SEATTLE
ROBERT GUTIERREZ, M.D.
NEW YORK
GERSHOM J. THOMPSON, M.D.
AND
JAMES T. PRIESTLEY, M.D.
ROCHESTER, MINN.
EGON WILDBOLZ, M.D.
BERNE, SWITZERLAND
AND
VINCENT J. O'CONOR, M.D.
CHICAGO

KIDNEY

Anomalies.—Dees [1] states that developmental anomaly of the kidney or the ureter is of clinical importance and that it occurred among 9.6 per cent of 1,410 consecutive patients for whom pyelograms had been made.

Renal anomaly accounts for much more than 9.6 per cent of diseases of the upper part of the urinary tract.

Symptoms of anomaly of the upper part of the urinary tract usually begin when the patients are between the ages of puberty and 35 years.

Of 135 patients who had renal anomaly, the anomaly was the definite cause of symptoms among 100; it was asymptomatic among 25 and was a questionable cause of symptoms among 10.

Infection was present in 50 per cent of the patients who had renal anomaly; calculus was present in 20 per cent and obstruction in 43.5 per cent.

The chief complaint of 62.2 per cent of the patients was pain of renal or ureteral distribution. The pain was caused by infection, obstruction

1. Dees, J. E.: The Clinical Importance of Congenital Anomalies of the Upper Urinary Tract, J. Urol. **46**:659-666 (Oct.) 1941.

or stone in the majority of cases; but it occurred also among 16 patients who had uncomplicated renal anomaly.

The incidence of hypertension in the group was not appreciably different from that which would be noted in an unselected group. In 3 patients, however, the congenital anomaly was felt to be the cause of hypertension.

Thirty-nine patients (29 per cent) required open operation on the kidney or the ureter for correction of the anomaly or its complications.

Shivers and Mathis [2] present a case representing complete unilateral duplication of the ureter and the pelvis complicated by a cystlike dilatation of the intravesical portion of the supernumerary ureter. This condition was not true ureterocele. Within this dilated portion of the ureter were three calculi. There was no evidence of dilatation of the ureter or the renal pelvis above the site of this obstruction. Histologic study of the tissue removed at operation disclosed that infection was not present, and the evidence pointed to an acute destructive process involving the wall of the ureter and probably, to some extent, the connective tissue of the wall of the bladder surrounding it. This acute process was brought about by mechanical irritation and interference with venous and lymphatic return drainage caused by the calculi. The rapid expansion of the terminal portion of the supernumerary ureter, together with the ability of the muscular structure of the upper part of the ureter and the pelvis to undergo work hypertrophy, probably compensated for any back pressure which may have existed and accounted for the absence of dilatation which might be expected to occur in the upper part of the ureter and the pelvis in the presence of an obstructive lesion in the lower part of the ureter.

Surgical Procedures.—Campbell [3] states that there is a conservative surgical treatment of certain renal diseases which are localized to one segment of a normally formed kidney or to a half of a reduplicated, a horseshoe or an otherwise bilaterally fused kidney.

In some instances, the remaining segment of the kidney will prove to be so small as to make resection an unwarranted or unjustifiable surgical risk; in such an instance nephrectomy is required. Occasionally, primary or secondary nephrectomy will be required because of surgical damage to the renal vascular supply.

With due care to adequate preoperative preparation by the administration of fluids, the use of urinary antiseptic agents and particularly

2. Shivers, C. H. deT., and Mathis, J. H.: A Clinical Study of Two Unusual Types of Renal and Ureteral Disease, J. Urol. **46**:1079-1099 (Dec.) 1941.

3. Campbell, M. F.: Resection of the Kidney, J. A. M. A. **117**:1223-1229 (Oct. 11) 1941.

the transfusion of blood, a gratifying number of both young and older patients can successfully undergo renal resection with conservation of a worth while amount of satisfactorily functioning tissue. The technic of and indications for the various procedures employed are to be considered. The mortality rate accompanying this operation is low, in view of the gravity of the surgical problem. Campbell reports that 2 deaths occurred in 41 cases of resection of the kidney. In 1 case, a child died who had an enormous cyst in the upper part of the pelvis in the right reduplicated portion of a horseshoe kidney. This death, four days after operation, was directly due to surgical trauma (largely, rapid evacuation of the cyst) and to hemorrhage from an aberrant vessel which entered the upper pole of the cystic kidney from a point high under the liver. The other death was attributable to infection of the wound in the loin.

When urinary infection is part of the urologic disturbance, the patient should not be discharged as cured after the operation until at least two negative cultures of an aseptically collected specimen of urine have been obtained.

Campbell has not found any notable changes in the blood pressure of patients who by operation are left with a half of a reduplicated kidney.

Surgical Complication.—Mathé and Faulkner [4] report a case of bilateral pneumothorax, mediastinal emphysema and extensive subcutaneous emphysema complicating nephrectomy for tuberculosis. The causative mechanical factors involved in the production of pneumothorax in their case probably were nicking of the visceral (diaphragmatic) pleura; tearing of the right and left mediastinal pleura; fracture of the eleventh rib by the kidney rest and puncture of the underlying lung and rupture of an obstructive emphysematous lung, an emphysematous bleb or tuberculous lesions.

Preexisting pathologic changes within the thorax, such as mobility and friability of the mediastinum and pleuropulmonary adhesions, play a definite role in the prevention or in the indirect production of operative pneumothorax.

The distinguishing feature in the general treatment of unilateral, bilateral, adherent and nonadherent types of pneumothorax is discussed.

Tuberculosis.—Braasch and Sutton [5] state that a diagnosis of bilateral renal tuberculosis was made among 291 (13 per cent) of 2,200 patients

4. Mathé, C. P., and Faulkner, W. B., Jr.: Bilateral Pneumothorax and Subcutaneous Emphysema Complicating Nephrectomy: Report of a Case, J. Urol. **46**:601-612 (Oct.) 1941.

5. Braasch, W. F., and Sutton, E. B.: Prognosis in Bilateral Renal Tuberculosis, J. Urol. **46**:567-578 (Oct.) 1941.

with renal tuberculosis observed at the Mayo Clinic during the years 1910 to 1934, inclusive. Eighty-seven of these 291 patients underwent nephrectomy; hence, 204 patients with tuberculosis did not undergo operation.

Nephrectomy in cases of bilateral renal tuberculosis is indicated only when there is a decided difference in the extent of the process in the two kidneys. Nephrectomy is usually not indicated unless the diseased kidney is the cause of symptoms requiring relief.

A clearcut history of a period of dysuria and frequent micturition many years prior to examination and a recent history of recurrence of symptoms frequently are elicited and are typical of bilateral involvement. When the disease is bilateral, cystoscopic examination usually reveals a greater degree of involvement of the bladder than is found when the disease is unilateral.

The previous occurrence of tuberculosis in other tissues often seems to increase the patient's resistance to renal tuberculosis and may be accompanied by a relatively good prognosis.

In spite of advanced bilateral involvement of both kidneys, the combined renal function often is normal or is only slightly reduced. Little subjective evidence of renal insufficiency was observed in many cases in which renal function was reduced greatly.

The incidence of hypertension in cases of bilateral renal tuberculosis is little higher than the average incidence of hypertension observed among adult persons.

The subsequent clinical course was traced in 167 cases in which definite clinical evidence of bilateral renal tuberculosis was present. The survival rate for patients traced after three years or more was about 72 per cent; for those traced after five years or more, 58 per cent; for those traced after ten years or more, 26 per cent, and for those traced after fifteen years, 16 per cent. Most of the patients who were living ten or fifteen years after examination were in fairly normal condition except for variable degrees of frequency of urination.

Therapeutic measures, such as treatment in a sanatorium or the advantages of rest, diet and sunshine, undoubtedly are factors in aiding longevity.

The authors declare that previous concepts concerning life expectancy in cases of nonsurgical renal tuberculosis demand radical revision. Unless the indications for nephrectomy are definite in a case of bilateral disease, they say, it would be well "to give nature a chance."

Thomas, Stebbins and Sandell [6] present reports of 4 cases of renal tuberculosis, in which the clinical data indicated that the tuberculous

6. Thomas, G. J.; Stebbins, T. L., and Sandell, S. T.: The Control and Arrest of Lesions of Renal Tuberculosis, J. Urol. **46**:579-589 (Oct.) 1941.

process in the kidneys had healed or had become arrested by means of an intensive hygienic regimen. The authors recommend hygienic treatment for all patients who have renal tuberculosis. Their opinion is that kidneys should and do react toward the destructive effect of Mycobacterium tuberculosis as do other organs and tissues.

Beach and Shultz [7] report 8 clinical instances of spontaneous healing of renal tuberculosis as signalized by nonrecurrent objective findings and lack of subjective developments over a prolonged period of observation ranging from six to fifteen years.

Diagnosis depended on recovery of Myco. tuberculosis from urine obtained from the kidney and specific identification of this organism. There was never any significant pyelographic change or deformity.

If the presence of Myco. tuberculosis in urine obtained from the kidney connotes tuberculous disease in a given kidney, then by the same token, disappearance of this organism from urine obtained from the kidney, without return of the organism for several years, should attest to healing of the erstwhile lesion or lesions, especially in the absence of symptomatic developments.

Since incontestable anatomic evidence avouches that usually only cortical healing occurs, the patients in the cases reported probably suffered cortical lesions.

There is no warranty that these cortical lesions under less favorable circumstances cannot undergo reactivation and extend into the medulla, only to culminate in renal or operative tuberculosis.

Ureterostomy for Renal Tuberculosis.—Higgins [8] states that the major complication which ensues after the performance of cutaneous ureterostomy is sloughing of that portion of the ureter which protrudes beyond the skin. Immediate application of warm saline dressing to the stump of the ureter and keeping it in place for several days after the performance of cutaneous ureterostomy may prevent such sloughing.

The ureter should not be stripped, because it must be made certain that an adequate blood supply to the ureter itself is maintained. Also, the ureter should be freed down toward the bladder as far as possible, so that tension on the portion of the ureter that protrudes beyond the skin can be avoided when the ureter is brought out at this site. This, of course, obviates the necessity of suturing the ureter to the skin and further impairing the blood supply. After cutaneous ureterostomy has been done, a small ureteral catheter should be passed up the pelvis of

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7. Beach, E. W., and Schultz, W. G.: Spontaneous Healing in Renal Tuberculosis, J. Urol. **46**:590-600 (Oct.) 1941.

8. Higgins, C. C., in discussion on papers of Smith,[29] Colby [27] and Creevy,[31] Tr. Am. A. Genito-Urin. Surgeons **34**:123-124, 1941.

the kidney and left in situ for a few days. The stump of the ureter and the catheter should be surrounded with moist saline dressings. This prevents leakage of urine at the operative site.

Stones.—Kjølhede and Lassen [9] state that on the basis of their own results of examination of kidneys in 135 cases in which necropsy was carried out as compared to the description by Randall himself of deposits of calcium on the papillae, they cannot see that Randall's papillary lesions are new pathologic entities.

In 86 of 135 cases in which necropsy was done, they found several kinds of deposits of calcium salts in the kidneys. In 14 instances, they discovered calculi in the kidneys, but only once did a papillary deposit of calcium salt seem to have contributed to the development of a coexisting calculus.

Since calculi often are found in kidneys without such deposition, the authors say that the deposits of calcium salt cannot be of essential significance in the genesis of calculi. In 4 cases, stone was found attached to the mucous membrane of a calix outside the renal papilla, but this stone had not developed from deposits of calcium there. Such deposits, however, are now and then encountered in the mucous membrane of a calix.

The deposits found occurred independently of the factors of sex and age of the patients affected, and also seemed to have had no relation to diseases of the gastrointestinal tract, the liver or the circulatory system; they were, however, encountered relatively often in association with such diseases as arteriosclerosis, infection or stasis in the kidneys.

Kjølhede and Lassen declare that according to Randall, it should be considered as proved that deposits of calcium on the surface of a renal papilla constitute the starting point of the formation of calculi. However, results of their study indicate clearly that such papillary deposits cannot be causes of any great significance in the genesis of calculi since it was possible in only 1 case in their series to demonstrate a calculus which might have been adherent to such a deposit. Their conclusion is that a deposit of calcium salts at the most can be a locus minoris resistentiae in the development of renal calculi but that such development most frequently is the result of other wholly different factors.

Derrah and Kaufman [10] present 2 cases in which calculosis of the right kidney was associated with obstructive jaundice. Obstructive jaun-

9. Kjølhede, K. T., and Lassen, H. K.: The Significance of Randall's Papillary Lesions in the Causation of Renal Calculi, J. Urol. **47**:45-57 (Jan.) 1942.

10. Derrah, B., and Kaufman, D. R.: Disease of the Right Kidney as a Cause of Obstructive Jaundice: An Anatomical Explanation, J. Urol. **46**:853-865 (Nov.) 1941.

dice and vague gastrointestinal symptoms without jaundice may be caused by renal disease on the right. The close anatomic relationship of the right kidney to the duodenum as well as the renal digestive reflex should be considered when an attempt is made to account for gastrointestinal symptoms of renal disease on the right.

Hyams and Kenyon [11] state that urinary calculi are not infrequently symptomless and are therefore overlooked. Since many calculi are present for a long time before detection, they are of large size when they are finally found and are accompanied by advanced changes in the kidney. A history of previous calculosis with persistent infection of the urinary tract by urea splitting organisms in spite of intensive treatment necessitates frequent urographic observation. As progress in medicine continues and as improved diagnostic measures are devised and routine roentgen studies are carried out, many instances of this type of calculus may be detected before irremediable damage has ensued.

Tumor.—Study of reports of treatment in cases of Wilms's tumor shows that there are well qualified adherents of three types of therapy: operation, radiation and a combination of operation and radiation. Dean [12] states that Wilms's tumor is so rare that the majority of urologists and pediatricians encounter it only occasionally, but he declares that they do recognize the seriousness of the condition.

Wilms's tumor is a congenital embryonic mixed tumor which originates from the anlage of the kidney. Depending on the stage of embryonic development at which the tumor arises, its structure may vary considerably in the degree of differentiation of its component cells and in the number of different tissues represented. These structural differences probably are the principal reasons for wide variations in the natural history and the radiosensitivity of Wilms's tumor and in the clinical course of the patient who has it.

Dean reports the results of the treatment of 8 patients. Widely different results were obtained. In view of clinical experiences such as he discusses in which the disease seldom follows the same course and responds so differently to similar forms of treatment, he is of the opinion that it is misleading to consider Wilms's tumor a clinical entity with a uniform mode of onset or a natural history which follows a common pattern and which regularly responds to the same treatment.

Since in most cases the disease is far advanced when the first symptom occurs, no time should be lost in establishing the diagnosis.

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11. Hyams, J. A., and Kenyon, H. R.: Silent Urinary Calculi, Urol. & Cutan. Rev. **44**:230-235 (April) 1940.

12. Dean, A. L.: The Treatment of Wilms' Tumors, Tr. Am. A. Genito-Urin. Surgeons **34**:75-79, 1941.

Excretory urograms, therefore, should be made whenever there is the suggestion of a mass in the region of an infant's kidney.

As soon as the primary tumor has been demonstrated, every part of the body should be searched for metastasis. If any is found, the patient cannot be operated on. The scalp seems to be a favorite site for early spread of the process. Even when the lungs appear to be normal at first, roentgenograms of the thorax should be made repeatedly every two to three weeks.

Dean expresses the opinion that the treatment of every Wilms's tumor should begin with irradiation. This should continue as long as the tumor shrinks. Since the minimal curative dose for individual tumors is unknown, it is essential to treat each patient without interruption to full skin tolerance. Although marked regression often occurs, the tumors always regenerate. Like many other therapeutic agents, external radiation must be given Wilms's tumor until the desired effect has been accomplished.

If radioresistance is demonstrated by failure of the tumor to regress after two weeks of daily irradiation, surgical intervention should be employed without further delay. The best operation for a large tumor seems to be carefully and gently performed transperitoneal nephrectomy after the vessels of the renal pedicle have been ligated. In addition to these principal vessels, a number of dilated veins are often found which pass from the periphery of the tumor to adjacent perirenal tissues. It is well to cut these between double ligatures. After removal of the kidney, a search should be made for extrarenal extension, but, as Dean's records show, they are not always discovered when they are present. For this reason it is wise to give radiation postoperatively.

Kirwin [13] presents and discusses a case in which the papillary tumor involved the renal pelvis. Complete nephroureterectomy was done, together with removal of a coned-out segment of that part of the wall of the bladder surrounding the ureter. Results achieved in his case provide ground for the belief that no time should be wasted in the application of roentgen therapy. Coutard's method of fractional dosage was attempted, but the patient proved unable to endure it.

Papillary carcinoma of the renal pelvis is a relatively uncommon form of neoplasm, although a steadily increasing incidence seems to be indicated by the number of reports concerning it which have appeared recently in medical literature. This is due, however, not so much to actual increase in the number of cases, as to improvements in urologic

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13. Kirwin, T. J.: Papillary Carcinoma of the Renal Pelvis, Surg., Gynec. & Obst. **73**:759-765 (Dec.) 1941.

diagnostic methods, which permit more frequent recognition of the lesion.

Hager and Schiffbauer [14] present a case in which a metastatic lesion in the wall of the chest became evident eight years before the primary renal adenocarcinoma was extirpated. The patient was well two years after removal of the primary and secondary tumors. "In all probability had our information been complete in the beginning, surgery might have been denied the patient," the authors write. They say that their experience bears out Barney's contention that "if a metastasis is apparently solitary and accessible to surgical removal, it is definitely worth while to undertake removal of the metastasis as well as the primary growth."

Foulds [15] records a case in which a renal tumor contained elements of malignant papillary cystadenoma and papillary carcinoma with clear cells. This case, with other reported cases, illustrates the transition from renal adenoma to malignant cystadenoma and eventually, in some instances, to papillary carcinoma with clear cells.

Polycystic Disease.—In a series of 58 patients with polycystic renal disease seen by Cahill and Fish,[16] operative procedures were carried out for 23. The age of these patients ranged from 3½ months to 74 years. The average age was 40 years.

Conditions in which operation is required may well be divided into six groups, as follows: (1) severe hemorrhage within or around the kidney, caused by physical trauma to the kidney, such as blows and falls or spontaneous rupture of cysts; (2) infection within or around the kidney; (3) obstruction to the flow of urine caused by pressure of cysts within the kidney or the ureters; (4) obstruction or pain caused by calculi; (5) tumors and tuberculosis which are producing actual destruction of the kidney, and (6) steadily increasing hypertension without other evidence of renal failure.

When polycystic renal disease has progressed to a point at which renal failure or impending renal failure is due to the disease itself, the prognosis is poor, and the results of most operative procedures are unsatisfactory. When symptoms, such as pain, hematuria, anuria, gastric

14. Hager, B. H., and Schiffbauer, H. E.: Silent Adenocarcinoma of the Kidney with Single Metastasis to the Chest: Report of a Case, Tr. Am. A. Genito-Urin. Surgeons **34**:1-7, 1941.

15. Foulds, G. S.: An Unusual Kidney Tumor: Malignant Papillary Cystadenoma and Papillary Carcinoma with Clear Cells, Tr. Am. A. Genito-Urin. Surgeons **34**:9-13, 1941.

16. Cahill, G. F., and Fish, G. W.: Surgical Aspects of Polycystic Kidney Disease, Tr. Am. A. Genito-Urin. Surgeons **34**:81-87, 1941.

distress and failing renal function, are due to factors not directly attributable to the disease itself, the prognosis is excellent. The results of surgical intervention are promising, often even dramatic, and the end results are of long duration.

The surgical procedures carried out in this group of cases were nephrectomy in 6 cases, incision and drainage of cysts in 14 and incision and drainage of perinephritic abscesses in 3 cases.

Two deaths followed operation; 1 death occurred two hours after operation, from shock, and 1 occurred fifty days after operation, from bilateral renal infection.

Follow-up data concerning the patients operated on are summarized as follows: Seventeen patients were alive and symptom free from one to sixteen years after operation; 2 patients died from renal failure three years after operation; 1 patient died from the same cause six years after operation, and 1 patient died seven years after operation.

Doolin [17] reports that death from uremia occurred in a case of polycystic kidney. In estimating the cause of the patient's death, Doolin concludes that the absorption of the extravasated proteins from the blood in a hematoma and in torn muscle and their subsequent excretion by the kidneys made too great a physiologic strain for these organs, which hitherto had responded without protest to the various strains which an active outdoor life had laid on them.

Polycystic kidney is divided into two types: One is the congenital type in which the persons who have it either are stillborn or die shortly after birth; the second afflicts adult persons and does not cause symptoms until after the twentieth year. Renal failure in the presence of the second type progresses slowly with long periods of survival.

Trauma.—Cheetham [18] reported 43 cases of severe trauma to the kidney. Twelve of the patients were treated medically; the condition of 9 was acute, and the condition of 3 was of the type illustrating the late effects of renal injury. In 31 cases operation was performed. In 5 of these relief was obtained by conservative surgical treatment. All the cases were of the type in which late complications of renal trauma are presented. Nephrectomy was necessary in 26 cases: in 9, because of the acute symptoms which followed immediate trauma and in 17, in which the condition was of the late type, because of a complicated aftermath. In the total of 43 patients treated there were no deaths.

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17. Doolin, W.: An Unusual Fatality from Uraemia, Brit. J. Surg. **28**:500-502 (Jan.) 1941.

18. Cheetham, J. G.: The Clinical Management of Renal Trauma: Collective Review, Surg., Gynec. & Obst. **72**:573-584 (June) 1941.

Gunshot Wounds.—Scholl [19] states that gunshot wounds of the kidney are usually secondary in importance to injuries of the adjacent viscera. In most cases, the situation of the wounds and the presence of hematuria are the first indications of renal damage. Hematuria is usually present, but the content of blood in the urine usually is not excessive in the majority of cases. In the early stages, hematuria tends to cease spontaneously after several days. Secondary hemorrhage into the bladder is fairly frequent. Cystoscopy and excretory urography are of little diagnostic aid in the presence of acute injuries. The immediate question to be settled is whether or not operative intervention is imperative. Physical observations, wound of entry, pain, swelling and hematuria generally determine the diagnosis and the situation of the lesion.

There are three possible surgical procedures in the care of wounds of the kidney. The first is drainage of the renal area, which permits inspection, evacuation of blood clots and control of bleeding. This is the most satisfactory procedure in most cases and is attended by the lowest mortality rate.

The second is composed of partial nephrectomy, renal repair and plastic operations, but these are not satisfactory in the case of open wounds. Partial procedures do not remove the cause of the bleeding and are rarely justifiable.

The third is nephrectomy, which may be necessary in some cases of persistent hematuria or in the presence of multiple lacerations of the parenchyma. It removes a potential field for infection and limits future bleeding from the operative site. Nevertheless, it is a difficult and hazardous procedure in the early days after injury, and most observers agree that only in rare cases is it indicated or advisable.

Pyelonephritis.—In a series of 72 patients reported on by Prather,[20] recurrent pyelonephritis of pregnancy appeared to have an incidence of 23 per cent. The incidence is definitely increased if the urine remains infected during the interval between pregnancies. If the urine becomes sterile during the interval between pregnancies, the chance of recurrent pyelonephritis becomes less than 1 in 5, whereas if the urine remains infected the ratio becomes 1 in 2. There appears to be no tendency toward hypertension during a succeeding pregnancy as the result of pyelonephritis during a previous pregnancy.

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19. Scholl, A. J.: Gunshot Wounds of the Kidney, Tr. Am. A. Genito-Urin. Surgeons **34**:65-73, 1941.

20. Prather, G. C.: Recurrent Pyelonephritis During Pregnancy, Tr. Am. A. Genito-Urin. Surgeons **34**:45-50, 1941.

Harrison and Bailey[21] state that asymptomatic urinary infections are much more frequent among patients who have diabetes than among those who do not. Asymptomatic urinary infections in the diabetic state may lead to serious lesions of the kidneys. Necrosis of renal tissue extends rapidly, once the infection gains a foothold. It is increased in some cases by centripetal propagation of thrombi which form about the areas of infection. A consideration of the end results of infection of the urinary tract among patients who have diabetes emphasizes the importance of treatment of the infection before irreplaceable tissues have been destroyed.

Perinephritis.—Toulson[22] states that perinephritic abscesses practically always are associated with pathologic conditions of some form in the kidney. The initiating lesion may be caused by an infection arising from the cortex alone or from pyonephrosis.

In Toulson's series of 41 cases of perinephritic abscess, an analysis was made to determine how many patients had demonstrable lesions of the kidney.

The anatomic characteristics of the perirenal tissues and the exposure of these tissues to renal infections make it seem that all perinephritic abscesses are secondary. Adhesions between the capsule of the kidney and the perinephritic tissues, a common operative finding, would lead to the belief that perinephritis, although it is not regularly diagnosed, is rather common.

In only 13 of this series of 41 cases could pyonephrosis or a destructive renal lesion be demonstrated. In 27 cases, the lesions were proved or assumed to have metastatic origin; in 1 case the lesion was caused by direct extension of tissue.

The onset of the symptoms varied in time from twenty-four hours to four weeks before admission of the patient to the hospital, the average being between ten days and two weeks. Chills, fevers, sweats, renal pain and other symptoms were accompanied by prostration, bulging of the loin and costovertebral tenderness and were present in practically all the patients. Those patients who had destructive renal lesions invariably had an elevation of the nonprotein nitrogen in the blood.

In most of the cases there was a definite roentgen finding of a mass on the affected side, concavity of the spinal column, obliteration of the shadow of the psoas muscle, elevation of the diaphragm and displacement of the colon and the ureter.

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21. Harrison, J. H., and Bailey, O. T.: The Significance of Necrotizing Pyelonephritis in Diabetes Mellitus, J. A. M. A. **118**:15-20 (Jan. 3) 1942.

22. Toulson, W. H.: Perinephritis and Perinephritic Abscesses, Tr. Am. A. Genito-Urin. Surgeons **34**:41-44, 1941.

Incision and drainage were all that was necessary to effect cure in practically all cases in which the condition was of metastatic origin. It was considered unwise to break up the walls of a well circumscribed abscess in order to try to deliver the kidney.

Nephrectomy was done in 5 cases in which perinephritic abscess was complicated by renal destructive lesions, and other renal operations were performed in the remaining 8 cases of this character. This was done even though a second operation was necessary.

Renal Hypertension.—Ravich [23] states that hypertension can be caused by increased peripheral resistance and ischemia within the kidney due to generalized toxic effects on the intrarenal circulation, such as occurs in cases of various types of nephritis. It may result also from mechanical compressive forces at or near the hilus of the kidney, producing renal ischemia, augmented back pressure against the general circulation and increased heart action.

The kidney in a normal adult person has been provided by nature with an extrarenal pelvis and a wide hilus. These act as efficient shock absorbers against renal ischemia and hypertension. A certain proportion of human beings, not so fortunate, are afflicted with a persistent fetal type of kidney, with its intrarenal pelvis and narrow hilus. Although in the lower animals this kind of kidney is not much of a handicap, in man, with his erect posture, such organs are vulnerable to various stresses and strains that lead to renal ischemia and hypertension. Because of the restricted space in the hilus of these intrarenal pelvic kidneys, even minor pathologic forces can do considerable harm. The increased mobility of the human kidney, due to the open inferior end of its fatty capsule, has an important influence on the patency of the large renal vessels at the hilus.

The renal circulation, which comprises a third of the entire blood volume, when impeded by the cramped hilus of an intrarenal pelvis creates a traffic jam within the blood stream as certain in its effects as that of a bottle neck on a highway. The resulting back pressure, Ravich says, increases the burden on the heart and results in hypertension.

In a series of 200 cases, Ravich was impressed by the regularity with which hypertension was accompanied by disease in intrarenal types of kidney pelves. On the other hand, because of the cushioning effect inherent in the extrarenal type, essential hypertension in such protected kidneys appeared extremely unlikely, even though the existing pathologic changes were of considerable degree.

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23. Ravich, A.: Hypertension: A New Clinical Concept of Its Etiology, J. Urol. **46**:641-658 (Oct.) 1941.

Since essential hypertension may exist for a long time without apparent impairment of renal function, the status of the kidney and its circulation as the source of the trouble is unfortunately usually overlooked. Careful interpretation and recognition of even mild abnormalities ascertainable by the making of so-called intravenous pyelograms are essential for early diagnosis and prophylaxis.

On the basis of examination of intravenous urograms, the physician should be able to make a long range forecast of hypertensive possibilities among patients who have intrarenal pelvic kidneys. This should be particularly interesting to statisticians of insurance companies in their studies of life expectancy and its relation to renal diseases. By recourse to the huge actuarial statistics maintained by these companies, it should be relatively simple for them to ascertain in what proportion, if any, of patients with extrarenal pelvic kidneys hypertension ever develops.

Allen [24] states that the typical effect of clamping or ligation of explanted kidneys is one of acute hypertension which persists throughout the period of asphyxia. This acute hypertension occurs also from asphyxia of only one kidney. It can be superimposed on existing chronic hypertension. Restoration of circulation is followed by a rapid decrease to the original pressure or even to a lower pressure.

The nervous character of this type of hypertension is evident from its occurrence during a time in which humoral factors from the kidney are excluded.

The nervous mechanism concerned in hypertension was investigated only to the extent of experiments carried out with the aid of general and local anesthesia. A psychic component is evidenced by the higher pressures of nervous excitable dogs when compared with the lower pressures of quiet passive ones. A definite although less marked hypertension still occurs when the psychic factor seems to be eliminated by anesthesia. The most probable interpretation of the available facts points to a nervous reflex element in the hypertension, which occurs as long as a reflex response is possible.

When renal asphyxia is continued for a period beyond any possible physiologic limits (e. g., six hours), rather brief secondary hypertension may ensue. Apparently this result does not occur except when the asphyxia of both kidneys or of one kidney has been so prolonged that it causes rapidly fatal intoxication. Possibly, therefore, any toxic asphyxial products noted in experiments of this type may be of postmortem character, so to speak, and not representative of anything occurring physiologically or clinically.

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24. Allen, F. M.: Acute Hypertension with Clamping or Ligation of Explanted Kidneys, J. Urol. **46**:834-852 (Nov.) 1941.

Results of the experiments with explanted kidneys, although involving complex factors, illustrate the complex control of blood pressure in the intact organism. Within time limits which reasonably can be considered physiologic (e. g., two to four hours), hypertension arising from substances supposedly produced during renal asphyxia either is nonexistent or is nullified by the predominant nervous control. Therefore, without denial of the reality or the value of the observations made under nonphysiologic conditions, warning should be given against attempts to expand what might be called artificial findings into a universal theory of hypertension.

Prinzmetal, Hiatt and Tragerman [25] reported a case of hypertension in which the patient had bilateral renal infarction. A woman 53 years old suffering from chronic rheumatic heart disease became hypertensive within the space of a few days after an acute attack of severe abdominal pain. Elevation of blood pressure was accompanied by increasing suppression of urine short of complete anuria and by progressive retention of nitrogen, and death occurred in the presence of uremia. At necropsy there were found occlusion of both main renal arteries by thrombus formation, probably of embolic origin, and almost complete infarction of both kidneys. Since the train of events was identical to that occurring in the experimental production of hypertension, this case offered a perfect example in a human being of hypertension resulting from acute renal ischemia.

Perfusates that were prepared immediately after death from one of the infarcted kidneys revealed the presence of a pressor substance which presumably is the same as that responsible for the hypertension that follows termination of complete renal ischemia in experiments on animals. Attention is called to hypertension as a neglected sign in occasional instances of renal infarction.

URETER

Transplantation.—Hinman and Weyrauch [26] state that the end of the implanted ureter constitutes an area of crucial importance in determination of the success or failure of ureterointestinal anastomosis. They carefully traced the pathologic changes which occur in this structure, especially with a view to demonstration of the hazards which accompany damage to the blood supply and the entrance of infection; if it extends above the site of the anastomosis, either anemic necrosis or infectious

25. Prinzmetal, M.; Hiatt, N., and Tragerman, L. J.: Hypertension in a Patient with Bilateral Renal Infarction: Clinical Confirmation of Experiments in Animals, J. A. M. A. **118**:44-46 (Jan. 3) 1942.

26. Hinman, F., and Weyrauch, H. M.: An Experimental Study of Uretero-Intestinal Implantation: V. The Destiny of the Implanted Ureter, Surg., Gynec. & Obst. **74**:129-136 (Feb. 1) 1942.

gangrene gives rise to fatal peritonitis. A virulent infection in the ureteral stump causes serious damage to the upper part of the urinary tract, first by acute ureteritis with its attendant stasis and later by the formation of stricture. The changes in the end of the ureter, therefore, play a great part in accounting for the morbidity and the mortality, both early and late, which attend the operation.

Colby [27] reports 10 cases of renal tuberculosis in which the ureters were transplanted to the skin. Advanced disease was present in all. In many there were genital lesions, active tuberculosis of bones and probably other areas of unsuspected disease, although there were no active pulmonary lesions. The operation of cutaneous ureterostomy entails little risk. No deaths resulted directly from the operation, although 1 patient died from a ruptured tuberculous ulcer of the small intestine before leaving the hospital. Simultaneous bilateral ureterostomy was done for 2 patients who had tuberculosis of both kidneys. Both died within a few months and neither was particularly benefited while alive. Considerable benefit from the operation was obtained for those patients whose remaining kidney was diseased after removal of the opposite tuberculous kidney. Their intolerable vesical symptoms were relieved, and the progress of renal damage was lessened. Five such patients, who had undergone ureterostomy, were alive and useful at the time of Colby's report. If the operative result is a rosette of ureteral mucous membrane which projects beyond the skin, there is reason to believe that patients can live comfortably without the need of catheters and that they can escape the formation of stricture at the skin, even in the presence of active renal tuberculosis. If this is true, these patients can easily care for themselves without the nuisance of changing of catheters, and the danger of pyelonephritis, secondary infections with urea-splitting bacteria and formation of stones is lessened. Transplantation of ureters to the skin, as usually performed, holds no guarantee of a satisfactory junction of skin and ureter. A simple method which may help to accomplish this is suggested. Cutaneous ureterostomy is the most effective method for relief of symptoms from the hopelessly infected tuberculous bladder.

Goldstein [28] reports 8 cases of ureterocutaneous transplantation. In 5 of the 7 cases in which a tumor was present, the carcinomatous bladder was allowed to remain, with no intention of removal of it because of the advanced stage of the carcinoma and the poor condition of the patient.

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27. Colby, F. H.: Cutaneous Ureterostomy in Active Renal Tuberculosis, Tr. Am. A. Genito-Urin. Surgeons **34**:101-114, 1941.

28. Goldstein, A. E.: Ureterocutaneous Transplantations, J. Urol. **46**:873-884 (Nov.) 1941.

The operation is simple and is applicable to all poor risk patients who have carcinoma of the bladder, when suffering is excruciating and all other measures have failed. The operation is applicable also to all patients who have diseased infected kidneys with dilated ureters, especially in association with carcinoma of the bladder. Three patients died within ten days after the operation. Three patients lived comfortably from eight to ten months after the operation. Two patients were still alive and comfortable thirteen and thirty months, respectively, after the operation.

In discussing ureteroenterostomy, Smith [29] states that the transplantation of normal ureters which drain uninfected kidneys does not constitute too great a risk to make the procedure prohibitive. Late results, especially among older people, are not too good. In the majority of patients in Smith's series of cases, one kidney at least showed evidences of faulty drainage. Calculi developed among 4 patients. Several patients had elevated values for nonprotein nitrogen—evidence of bilateral renal insufficiency.

Infection and dilatation of the upper part of the urinary tract which so commonly accompany carcinoma of the bladder constitute a definite hazard and warrant transplantation of the ureters to the skin rather than to the bowel.

The clearest indication for ureteroenterostomy is exstrophy of the bladder; incurable vesicovaginal fistula, unless it is accompanied by radiation changes and urinary infection, is also a valid reason for this operation.

Poth [30] discusses implantation of the ureters into the rectosigmoid and reviews the postoperative course of patients who underwent the procedure. His operation of implantation of the ureters is divided into two stages; in the first stage, the ureter is embedded in the wall of the bowel without interruption or diversion of the urinary stream, and in the second stage, the opening is made between the ureter and the bowel, with diversion of the urinary stream into the intestine. At the first operation, the ureter is freed, the serosa of the rectosigmoid is split, the ureter is placed in the opening left by the serosa, and the serosa is covered over the ureter. At the next procedure, the partition between the ureter and the sigmoid is cut away by an ingenious device consisting of a cutting wire assembly. The lower end of the distal segment of the ureter is then cut off and inverted into the bowel.

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29. Smith, G. G.: Indications for Uretero-Enterostomy, Tr. Am. A. Genito-Urin. Surgeons **34**:93-99, 1941.

30. Poth, E. J.: Implantation of Ureters into the Rectosigmoid with a Study of the Postoperative Course, Surg., Gynec. & Obst. **74**:221-226 (Feb.) 1942.

Obstruction.—Creevy [31] states that noncalculous obstruction at the ureteropelvic junction is usually caused by stricture, by distortion, by peripelvic fascia or by neurogenic dysfunction.

A plastic operation is indicated when the kidney contains enough normal tissue to sustain the life of the patient. It is especially indicated for young persons and for those who have bilateral lesions. Creevy says that the most satisfactory operation for this condition is what he calls the Y plasty of Schwyzer and Foley.

Creevy reports 5 examples of uncommon types of obstruction, including 1 case of granuloma and 3 of polyps of the mucosa at the junction, and 1 instance of obstruction of the pelvis itself by accessory vessels after Y plasty. Four patients were treated by Y plasty and 1 by excision of the redundant pelvis and reimplantation of the ureter.

The occurrence of polyps contraindicates any operation which does not include careful exploration of the mucosa of the ureteropelvic junction. When accessory vessels cross the ureteropelvic junction, they should be excised even though a plastic procedure may leave them well above the junction, since they may later embed themselves in the pelvis and reproduce obstruction.

Pyoureter.—Davison [32] reported a case in which pyoureter and periureteritis occurred seventeen years after nephrectomy for calculous pyonephrosis. The stump of the ureter contained a calculus. No genitourinary or other symptoms referable to the process had been present during these seventeen years. Surgical removal was carried out successfully.

Davison states that it is important to determine at the time of nephrectomy whether or not the ureteral orifice in the bladder will remain patent. If because of the presence of a calculus or stricture, free drainage into the bladder is prevented, complete ureterectomy should be carried out to obviate future infection and empyema in the ureteral stump.

Stricture.—Spastic ureteritis [33] is a clinical entity which is similar in symptomatologic aspects to true organic stricture of the ureter but which can be distinguished from it by the prompt relief afforded by simple dilation. The condition should be suspected among all patients, particularly women, who present symptoms of vague abdominal pain, asso-

31. Creevy, C. D.: Unusual Types of Obstruction at the Ureteropelvic Junction, Tr. Am. A. Genito-Urin. Surgeons **34**:115-122, 1941.

32. Davison, S.: Pyoureter Seventeen Years After Nephrectomy, J. A. M. A. **118**:137-138 (Jan. 10) 1942.

33. Walther, H. W. E., and Willoughby, R. M.: Spastic Ureteritis (Ureteral Stricture): Essential Clinical Considerations, J. Urol. **46**:671-683 (Oct.) 1941.

ciated with varying degrees of urinary disturbance, not demonstrably due to disease in some other organ.

Dilation of the ureter, repeated as necessary, relieves most patients promptly. In the occasional case, surgical intervention may prove to be necessary.

It is now rather generally recognized by urologists that there is such a thing as painful stenosis or a spastic condition of the ureter. Opinions differ as to its frequency and its causation. There is little difference of opinion, however, as to the clinical picture, regardless of the causative factors, and there is a rather general belief in the efficacy of ureteral dilation as a means of relief from it.

Stone.—Finney [34] discusses the principle of the application of traction in the treatment of ureterolithiasis. His technic is simple. In all but 5 of 50 cases, the stone was removed with a homemade instrument, so to speak, constructed as follows: A no. 6 French x-ray catheter with either a whistle tip or a taper tip is modified by the insertion of a silk suture in the distal end, care being taken to tie the knot so that it becomes as small as possible. A wire stylet should be inserted to stiffen the catheter, which at this stage is ready for use. The catheter, with thread attached, is passed transvesically to the stone and beyond it, if possible. If the catheter will not pass, a local anesthetic agent is injected, and afterward a few drops of liquid petrolatum are utilized for lubrication. In nearly every instance, the catheter will then pass with little difficulty.

The thread-bearing catheter is moved onward until the renal pelvis is reached. At this point the stylet is withdrawn a few inches, and the cystoscope is removed; the catheter is left in place. By pushing toward the kidney with the catheter and pulling away from it with the suture, the urologist can make a loop without difficulty or injury. There is plenty of room in the dilated renal pelvis. Once the loop has been made, thread and catheter are pulled down the ureter together, until the stone is engaged in the loop. No doubt will be experienced as to when this occurs, since firm resistance is encountered.

The urologist is now in a position to exert as much traction as he wishes on the stone, for the loop rarely slips. It is best not to use traction greater than 1 or 2 pounds (0.5 to 0.9 Kg.), and an attempt should never be made to remove the stone immediately. A small scale is attached to the end of the catheter; the patient is put to bed, and pain is controlled by administration of an opiate. The nurse is instructed to exert traction of 2 pounds (0.9 Kg.) on the scale and to maintain it for a moment, every hour or two, for twenty-four hours. At the end

34. Finney, R. P.: The Principle of Traction in the Treatment of Ureterolithiasis, J. A. M. A. **117**:2129-2131 (Dec. 20) 1941.

of that time, the patient is anesthetized lightly with gas, and traction up to 5 pounds (2.3 Kg.) is exerted.

In Finney's series of 50 cases, the stone was obtained at the end of twenty-four hours in 47. Treatment was continued in the 3 cases in which calculi were refractory to the procedure and was successful in 2, in which the stone was passed within thirty-four and forty-two hours, respectively. The treatment in the third case was a failure. Having kept the loop in place for seventy-two hours without budging the calculus, Finney removed the calculus by open operation.

Livermore [35] sounds a note of warning concerning intraureteral manipulation. Pointing out that he himself devised an instrument for dislodgment of ureteral stones, he condemns all metal instruments for promoting the removal of stones in the ureter. The ureter is easily damaged, he says, and since the introduction of American catheters, which are much stiffer than the ordinary catheter that has been used, puncture of the ureter is becoming much more frequent. He states that Heckel recently reported 15 cases in which the ureter had been punctured. After an experience of thirty years in urologic practice, Livermore encountered his first puncture of a ureter while he was using one of the stiff catheters in question. The patient had a stone in the ureter, and an attempt was being made to pass the catheter beyond it. He suggests that the pressure of a stone might produce spots of necrosis or chronic inflammatory reactions, and hence, if his suggestion is valid, the ureter would be much more susceptible to damage than otherwise.

Bumpus [36] states that in the manipulation of ureteral stones the condition confronting the urologist is urinary obstruction associated with infection, a combination that can result in the most serious of consequences. He emphasizes the dangers of infection in the presence of obstruction. Severe febrile reaction under these circumstances is likely to occur rapidly as a result of renal involvement, and septicemia not infrequently follows. For this reason, it seems imperative that the urologist inform the patient of these dangers before he attempts manipulation and obtain permission of the patient to resort to surgical removal of the stone immediately if such untoward symptoms develop.

BLADDER

Tumor.—Young [37] discusses intravesical resection of the wall of the bladder and the peritoneal coat for certain tumors of the bladder and

35. Livermore, G. R., in discussion on Finney.[34]

36. Bumpus, H. C., Jr., in discussion on Finney.[34]

37. Young, H. H.: Intravesical Resection of the Bladder Wall and Peritoneal Coat for Certain Bladder Tumors, Tr. Am. A. Genito-Urin. Surgeons **34**:183-189, 1941.

reports a case. The operation is an extension of the technic of transvesical radical removal of tumors of the bladder together with a large portion of the wall of the bladder and the peritoneum covering it, and it appears to be the ideal method for radical removal of tumors in that region. For tumors which extend down the ureter and invade the bladder, as was the situation in the case described by Young, extension of the transvesical peritoneal technic is shown to be easy.

Young stresses the importance of removal of the peritoneum covering the wall of the bladder in resection for tumor of the posterior wall. It has been shown to be possible to operate entirely intravesically, without first entering the peritoneal cavity, after a wide suprapubic incision has been made in the midline and after insertion of a four-bladed, self-retaining retractor. This provides such wide exposure of the bladder that it is easy to pick up the mucosa at points distant from the tumor and to excise the entire wall of the bladder with its peritoneal coat and to close the defect extraperitoneally through the bladder. In the case reported in detail, it also has been shown that this same technic can be employed effectively for removal of a ureteral tumor which has grown into the bladder.

Colby [38] states that at the Collis P. Huntington Memorial Hospital, in Boston, work has been carried on for about four years with the supervoltage unit. He and his associates there have tried not to be overenthusiastic about the treatment of tumors of the bladder by supervoltage radiation and have carefully guarded against creating any impression that such a procedure might be curative in its effects on tumors of the bladder.

The communications of Colby and associates in the past have shown that among approximately 50 per cent of the patients treated adequately with supervoltage radiation, the tumors have definitely regressed, i. e., the tumors have been reduced to approximately a third or a half of their original size. Among about 33 per cent of the patients, the tumors have at one time or another actually disappeared completely, as far as could be determined by cystoscopic examination. This, however, was not by any means regarded as signifying cure.

At the time of their writing (1941), Colby and associates had approximately 70 patients who were adequately treated and whose course thereafter was carefully followed. Among about 50 per cent of the patients, well marked regression of the tumors occurred, and among about a third of the patients, actual disappearance of the tumors was

38. Colby, F. H., in discussion on papers of Barringer, Nesbit and Cummings,[47] Hamer and Wishard [58] and Wishard,[59] Tr. Am. A. Genito-Urin. Surgeons **34**:272-273, 1941.

noted. In many instances, the tumors eventually recurred. Among only a few of the patients the tumors remained absent from the bladder for periods long enough to afford any hope that certain tumors might be cured by external radiation. Colby considers such a possibility doubtful. On the other hand, he says, the observer cannot but gain the impression that if a little more could be added to treatment by external radiation, some of these tumors might be eradicated. He says that is what he and his associates were trying to do during the year prior to the time of his report.

He states that patients receive a preliminary course of external radiation, which usually is 8,400 r. If at the end of three weeks there has been a noticeable well marked regression of the tumor, then interstitial radiation by the implantation of gold radon seeds is added to the procedure, before the tumor has had an opportunity to receive the effect of the external radiation. Then, if the situation warrants it, the patient receives another 2,800 or 3,600 r of external radiation.

Tumors of the bladder will regress in entirely different ways, Colby reports. Regression is usually expected to take place within four or five weeks. This, however, is not true of all tumors, a fact that is well illustrated by the course of 1 patient who about a year prior to the time of Colby's report received a preliminary course of external radiation for an epidermoid carcinoma about 3 cm. in diameter, situated on the floor of the bladder. The tumor did not regress under radiation after the first course, and the patient received a second course, which amounted to a total of 12,000 r—a good preliminary course of radiation. Again there was no evidence that the tumor was regressing. Total cystectomy, with ureteral transplantation, was carried out, and the patient died in about ten days of an infection of the blood stream. At necropsy it was seen that the tumor had regressed to a diameter of only about 1 cm., and study of histologic sections disclosed only small nests of active tumor cells, with much fibrosis. In other words, the tumor, in the meantime, had undergone such marked regression that Colby thinks that he and his associates were not justified in attempting any such radical procedure as total cystectomy. If some type of interstitial radiation had been added to the treatment of this patient, Colby says, the patient would have had a much better chance of recovery.

Amyloidosis.—Rusche and Bacon [39] report 2 cases of amyloidosis of the urinary bladder, each substantiated by adequate proof of the pathologic lesion.

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39. Rusche, C. F., and Bacon, S. K.: Solitary Tumor-Like Amyloidosis of he Urinary Bladder, Tr. Am. A. Genito-Urin. Surgeons **34**:163-168, 1941.

After a review of the literature, Rusche and Bacon conclude that solitary tumor of amyloid in the urinary bladder is one of the rarest pathologic lesions. Clinically, they state, this lesion is confused with neoplasm; however, it can be readily identified by means of special stains for amyloid. The literature contains 3 cases of amyloidosis of the urinary bladder, 4 cases of amyloidosis of the urethra and 1 case each of amyloidosis of the renal pelvis, the seminal vesicle and the wall of the ureter.

Interstitial Cystitis.—Pool and Crenshaw [40] report on 34 patients who had interstitial cystitis treated by means of irrigation with silver nitrate in solution. They give a preliminary review of their results. At the time of their report, none of the patients had failed completely to respond to this therapy, except those concerning whom the diagnosis of interstitial cystitis was not definite. In other words, all except 1 of those patients whose condition was typical made satisfactory progress. This 1 patient had improved and was without pain but still continued to have moderate frequency of urination when last seen. Pool and Crenshaw emphasize the fact that they cannot state positively that any of their patients were cured, although their symptoms were relieved.

Their method of procedure is different from that advocated by other authors. Other physicians employ strong solutions immediately and then rely on local anesthesia or sedative agents for control of the pain which is caused when a 0.25 or 0.5 per cent solution of silver nitrate is used. Crenshaw and Pool prefer to begin the treatment with a dilute solution (1 : 5,000) and to increase the strength daily until a solution of 1 per cent has been reached. When the stronger solutions are used, the bladder is thoroughly lavaged with the solution each time, and then 2 fluidounces (59 cc.) of the solution is allowed to remain in the bladder for five minutes. At the end of this time, the bladder is emptied by means of a catheter.

Hunner's Ulcer.—Kreutzmann [41] discusses the treatment of Hunner's ulcer with roentgen therapy. A group made up of 5 women and 1 man received deep roentgen therapy over the region of the bladder in doses varying from 1,200 to 4,200 r. No change was noted in the man or in 2 of the women. In 3 of the women there was complete relief of symptoms with disappearance of the ulcer for periods ranging from seven to twelve months. In no case was permanent cure obtained. The

40. Pool, T. L., and Crenshaw, J. L.: Treatment of Interstitial Cystitis with Silver Nitrate, Proc. Staff Meet., Mayo Clin. **16**:718-720 (Nov. 5) 1941.

41. Kreutzmann, H. A. R.: The Treatment of Hunner's Ulcer with Deep X-Ray Therapy, J. Urol. **46**:907-912 (Nov.) 1941.

disadvantages of this form of therapy are the limitation of dose and the production of the menopause in women.

Simple Ulcer.—Boyd [42] states that ulcers of the bladder other than those resulting from cancer, syphilis, trauma and radiotherapy have been reported, but not often, in the literature. The terms employed to distinguish these ulcers have been varied. They have been called "simple chronic ulcer," "perforating ulcer," "the ulcer of interstitial cystitis" and "incrusting ulcer." To the ulcers designated by these terms is added an ulcer caused by staphylococcic infection of the bladder.

The causative factors mentioned have been trophic changes in the wall of the bladder, metastatic infection of the mucosa or the submucosa, obliteration of some of the small blood vessels of the mucosa by various processes and infection of the bladder by staphylococci and other organisms.

Schulte reported an ulcer of the bladder much like the one recorded by Boyd. It seemed to be caused by a strain of staphylococci which in experiments with the inoculation of animals had a definite tendency to produce lesions of the urinary tract rather than lesions elsewhere. In 1 animal, this strain produced an ulcer of the bladder like the one found in the patient.

In Boyd's case, the patient was a young man of 20 years who for five years before the ulcer appeared had had increased arterial tension, orthostatic albuminuria and general malaise. Eighteen months earlier, bilateral hydronephrosis had been found, but the bladder was normal. Six months later, the bladder was infected by staphylococci and Streptococcus faecalis, but no urinary symptoms were present. Severe bleeding persisted for ten days after cystoscopy, but the ulcer was not seen. About ten months later, an ulcer was found on the posterior wall of the bladder, where the wall protruded to overlie the region of the ureteral ridge. This protrusion was more or less fixed. The ulcer was about 5 cm. in diameter; it was shaggy, had a red base and fairly well defined edges and was elected a little above the surrounding mucosa. The ulcer was excised.

Postpartum Studies.—In a series of 116 cystoscopic examinations of the bladders of women in the postpartum period, Bennetts and Judd [43] found general relaxation and minor degrees of mucosal edema. Ecchymosis of the mucosa of the bladder was present to a minor degree in 12

42. Boyd, M. L.: Ulcers of the Bladder: The Report of a Case of Unusual Ulcer of the Bladder of Unexplained Origin, Tr. Am. A. Genito-Urin. Surgeons **34**:145-161, 1941.

43. Bennetts, F. A., and Judd, G. E.: Studies of the Post-Partum Bladder, Am. J. Obst. & Gynec. **42**:419-427 (Sept.) 1941.

per cent of the cases and to a moderate degree in 4.3 per cent of the cases. The prevalence of these conditions was not increased by breech extraction nor were the conditions seen in 2 cases in which delivery was achieved by the midforceps operation, 1 case in which the procedure was version and extraction and 1 case in which low cervical cesarean section was done. Cystometric studies revealed hypotonic bladders with decreased bladder sensation and increased capacity in 86.2 per cent of the entire series. Type of delivery, trauma and the use of analgesia prior to delivery do not explain this dysfunction.

Fistula.—Ewell and Jackson [44] discuss vesicointestinal fistula, stating that it may occur among persons of any age but that it is more common among those between the ages of 40 and 70 years. Among infants and young children, it is practically always congenital in origin. It is approximately three times more common among men than among women, probably because of the presence and the position of the uterus and because of the less frequent occurrence of diverticulitis of the sigmoid among women. In Ewell and Jackson's series of 11 cases, the youngest patient was 26 years old and the oldest 72.

The causative factors of vesicointestinal fistula are: (1) congenital, usually associated with anal anomalies, (2) traumatic, of which surgical procedures account for approximately half, gunshot wounds being the next most common cause, (3) inflammatory, in which group diverticulitis of the sigmoid is the most common and (4) neoplastic. In the fourth type, in which are included the causes of approximately 20 per cent of all cases, carcinoma of the rectum, carcinoma of the sigmoid and carcinoma of the bladder are most common and occur in the order named.

Fistulas between the rectum and the bladder and between the sigmoid and the bladder may occur in about equal numbers.

The fistula is a direct passage when it is due to a neoplasm; when it is secondary to inflammatory disease, it nearly always develops after the formation of a localized abscess and is usually a tortuous tract.

The symptoms in a given group of patients are variable. In those cases in which the fistula is due to diverticulitis of the sigmoid, the onset is generally gradual, with repeated attacks of tenderness and pain in the lower left part of the abdomen and cramps due to the diverticulitis. These attacks may be accompanied by recurrent attacks of cystitis. Pneumaturia and the passage of feces per urethram are usually spoken of as being pathognomonic of vesicointestinal fistula. Certainly this is true of the passage of fecal matter. The passage of urine per rectum is another cardinal and frequent symptom of vesicointestinal fistula.

44. Ewell, G. H., and Jackson, J. A.: Vesico-Intestinal Fistula, J. Urol. **46**:693-698 (Oct.) 1941.

In a few cases, the history alone will be a sufficient basis for a diagnosis. Cystoscopy, excretory urography, the making of cystograms, gastrointestinal studies carried out with the aid of roentgenograms and proctoscopic examinations all should be done. Of these, cystoscopy is probably the most valuable. In a few cases, an unsuspected fistulous opening in the bladder has been found at cystoscopy. Frequently, the opening in the bladder is not seen, being obscured by an ulcerated or granulomatous area. Probing of the area with an x-ray ureteral catheter should be done cautiously to avoid creation of a fistula. Bubbles of gas or fecal matter extruding into the bladder may be observed.

In most cases, a surgical procedure of some type is required. The importance of performance of preliminary colostomy, of a type that will result in prevention of spilling of the fecal current from the upper segment into the lower segment of the colon, and the allowance of adequate time for the inflammatory reaction to subside, cannot be overemphasized. Colostomy should be carried out as close to the fistula as possible, so that a redundant loop of bowel above will not remain.

Because of the nature of the lesions which cause vesicointestinal fistula, the prognosis usually is grave, and the necessity for multiple operations creates a high operative mortality rate. Spontaneous healing rarely occurs in these cases. In the traumatic and postoperative types, a more favorable outcome may be anticipated. In a small percentage of cases, the lesion may heal spontaneously. In the remainder the condition usually is amenable to surgical treatment. Recurrence after operation has been reported in a few instances. The literature reveals that approximately a third of the patients are cured.

Irradiation Injury.—Dean and Slaughter [45] state that the bladder not infrequently is injured by irradiation of the uterus. Although uterine diseases commonly are treated by means of several types of irradiation, the greatest damage to the bladder follows applications of radium. Interstitial fibrosis occurs in the wall of the bladder, and obliterative endarteritis occludes nutrient arteries. Because these changes usually are slow, patients are likely to experience no distress referable to the bladder for a number of years after the uterus has been treated. For this reason, these injuries to the bladder occur almost exclusively among patients cured of the primary uterine disease.

The onset of symptoms is sudden. The patients suffer acutely from frequency of urination, dysuria and hematuria. Cystoscopic examination usually reveals single areas of ulceration surrounded by acute inflam-

45. Dean, A. L., and Slaughter, D. P.: Bladder Injury Subsequent to Irradiation of the Uterus, J. Urol. **46**:917-924 (Nov.) 1941.

mation. Both the mode of onset and the cystoscopic picture suggest carcinoma.

Dean and Slaughter have found that sulfanilamide and its derivatives, appropriately chosen on the basis of results of culture of urine obtained from the bladder, produce prompt relief. This is in marked contrast to the unsatisfactory results of previous therapy.

Dean and Slaughter state that it is interesting to note that the symptoms subside as infection is eliminated. Women whose urine is sterile can be rather comfortable, even though ulcerated areas of considerable size persist.

Thompson,[46] in discussing Dean and Slaughter's paper on injuries to the bladder subsequent to irradiation of the uterus, states that the time of the development of an irradiation injury is important. Many urologists are not aware of the fact that an irradiation injury of the bladder can appear many years after irradiation of the uterine cervix. For this reason, the diagnosis of the lesion is likely to be inaccurate. The urologist will conclude that the process that he sees in the bladder is an extension of the original malignant lesion. A poor prognosis frequently is offered and incorrect treatment is instituted in that further irradiation and sometimes the implantation of radon seeds has been advised in such cases. This leads to further insult of the tissues and ultimately to perforation and a distressing and unnecessary complication. Biopsy of material obtained from the edge of the lesion is desirable. Taking material from the central portion of the lesion will result only in obtaining necrotic fragments of tissue with which the pathologist cannot work. Treatment is important. The main part of the treatment is lavage with the proper solutions and the use of antiseptic agents. Careful curettage of these incrusted ulcers also has been employed, since most of them are incrusted. The urologist must be careful in performing curettage, for the bladder can be perforated easily.

Retention.—Nesbit and Cummings[47] state that in many cases urinary retention which follows surgical procedures is entirely functional or reflex in origin, since it occurs regularly among patients who are free from organic disease of the urinary tract.

Efforts have been made to prevent as well as to combat postoperative ileus and atony of the bladder by parasympathetic stimulation. Various drugs are known to have this pharmacologic action. There are three

46. Thompson, G. J., in discussion on papers of Dean and Slaughter[45] and Graves and Guiss, J. Urol. **46**:949-950 (Nov.) 1941.

47. Nesbit, R. M., and Cummings, R. H.: The Use of Prostigmine in the Management of Postoperative Urinary Retention, Tr. Am. A. Genito-Urin. Surgeons **34**:257-260, 1941.

main groups of parasympathomimetic agents: (1) the choline esters, such as acetylcholine, acetylbetamethylcholine (mecholyl) and carbaminoylcholine (doryl); (2) the inhibitors of cholinesterase, such as physostigmine and prostigmine, and (3) the older alkaloids, such as pilocarpine, arecoline and muscarine.

Prostigmine has been recommended because of its low toxicity and because of its alleged proved value.

Gordon, the authors note, reported a series of 85 cases in which prostigmine methylsulfate was used. Fifty of the patients were given a prophylactic dosage before and after operation, the procedure being administration of 1 cc. of a 1:4,000 solution at intervals of two hours, for six doses. Only 2 patients of this group required catheterization. This 4 per cent incidence of atony was compared to an 18.5 per cent incidence of catheterization computed in a control series of 318 cases. Marden and Williamson, the authors state, reported a series of 247 cases in which the patients received prostigmine methylsulfate. Ninety-eight of Marden and Williamson's patients received prophylactic doses of prostigmine methylsulfate; the incidence of postoperative catheterization was 5.1 per cent.

Nesbit and Cummings made observations in a small series of patients treated in the University of Michigan Hospital in an effort to determine the usefulness of prostigmine methylsulfate in the prevention of urinary retention. Patients who had undergone simple appendectomy, herniorrhaphy and anal operations were selected as constituting an ideal group for this study. In a control series of 285 cases, the incidence of postoperative catheterization was 17.5 per cent.

Prostigmine methylsulfate was given in 65 cases. The drug was used in two different ways: (1) as a prophylactic agent and (2) as a therapeutic agent in the treatment of postoperative urinary retention.

The incidence of catheterization was not materially influenced by the prophylactic use of prostigmine methylsulfate in their group of patients.

Prostigmine methylsulfate used as a therapeutic agent for impending retention was given to 13 patients. These patients received 1 cc. of a 1:2,000 solution of prostigmine methylsulfate each hour for four hours, or until the patient voided. Three of the patients (23 per cent) treated in this way required catheterization. The remaining 10 patients voided spontaneously.

In other words, in the clinic in which the authors made their study, in a carefully controlled small series in which prostigmine methylsulfate was given, the value of this drug in materially reducing the expected incidence of catheterization after major surgical procedures was not demonstrated.

Neurogenic Bladder.—Evans,[48] in discussing the physiologic basis of the neurogenic bladder, states that there are certain practical considerations which should be stressed.

First, the musculature of the bladder should never be allowed to stretch unduly, for if this happens, stretched muscle fibers result, and these fibers, like those of stretched skeletal muscles, are then less well able to respond to nervous activity.

Second, a stretched wall of a bladder is more likely to become infected than one that has not been stretched. Infection followed by fibrosis leads to impairment of vesical function and interferes with the resumption of motor activity when nervous control is restored.

Third, the musculature of the bladder is subject to and can be benefited by passive exercise just as is true of skeletal muscle. Such passive exercise can be accomplished by the employment of tidal drainage.

Nesbit and Gordon[49] state that autonomous neurogenic bladder results from destructive lesions of the conus terminalis and the cauda equina. Since the internal vesical sphincter shares in the hypertonic process which affects the bladder, it acts as an obstruction to the egress of urine. As with any obstruction of the outlet, decompensation of the bladder and damage to the upper part of the urinary tract ultimately will result if the condition persists sufficiently long. Modern treatment of the autonomous neurogenic bladder attempts to relieve the obstruction of the outlet. Presacral neurectomy has not proved to be satisfactory in Nesbit and Gordon's experience. Transurethral sphincterotomy yields more gratifying results, particularly if it is undertaken before the bladder has become decompensated.

PROSTATE GLAND

Hypertrophy.—Fowler[50] reports 5 cases in which prostatic obstruction occurred among young adult persons. The youngest was 19 years old; the oldest was 26. They presented in varying degree the characteristic symptoms of prostatism; difficulty in voiding, delay in the start of urination, voiding of a small stream, requirement of a longer time than normal for completion of the act; frequency, urgency and dysuria; overflow incontinence and complete retention. In 3 cases, gross enlargement of the prostate gland was found on rectal examination; in 2,

48. Evans, J. P.: The Physiologic Basis of the Neurogenic Bladder, J. A. M. A. **117**:1927-1930 (Dec. 6) 1941.

49. Nesbit, R. M., and Gordon, W. G.: The Surgical Treatment of the Autonomous Neurogenic Bladder, J. A. M. A. **117**:1935-1936 (Dec. 6) 1941.

50. Fowler, H. A.: Prostatic Obstruction in Young Adults, J. Urol. **47**:16-30 (Jan.) 1942.

the prostate gland was essentially normal in size. The diagnosis was confirmed by cystoscopy in 4 cases. In 1 case, in which the patient was a man 23 years old who had acute retention, it was impossible to reach the bladder with any urethral instrument.

One of Fowler's patients was a man 26 years old for whom fulguration of the obstructing lobe was carried out with a good result. The second patient was a man 23 years old who was treated by the making of multiple incisions from within outward through both lobes; this produced amelioration of his symptoms. This patient and 1 other underwent resection of the prostate gland. The fifth patient was treated by urethral dilation.

Rusche and Bacon [51] report 4 cases in which radical repair of recto-urethral fistula was carried out after perineal prostatectomy. Infection caused by Clostridium welchii developed in 1 patient after perineal prostatectomy; the patient recovered. In 2 instances, rectal injury was not recognized at the time of perineal prostatectomy. Suprapubic cystostomy is necessary as a preliminary step in the repair of rectourethral fistula. The success of the perineal operation is dependent on complete mobilization of the rectum to a point above the site of the fistula, resection of a cuff of rectum and anastomosis of the rectum to the skin without tension. Section of the rectal sphincter musculature is not indicated.

Emmett [52] reports a case in which urinary incontinence had been present for fifteen years in a patient with tabes. He says the incontinence was relieved by transurethral resection and states that many patients with vesical dysfunction (heretofore called "cord bladder") can be helped or completely relieved by transurethral resection of the vesical neck. This is especially true of patients who have a neurologic lesion which affects chiefly the sensory nerves, the classic example of which is the patient who is afflicted with tabes dorsalis. A bladder weakened from distention resulting from impairment of the sensory nerves which supply the bladder is more easily obstructed than a normal bladder. Because of this, minimal degrees of obstruction at the neck of the bladder which ordinarily would cause no difficulty may be the cause of vesical dysfunction associated with large quantities of residual urine in the tabetic type of bladder.

The patient, a man of 66 years, had had urinary incontinence for fifteen years. A short time before he was seen, the incontinence had changed to retention, requiring catheterization. The incontinence was

51. Rusche, C. F., and Bacon, S. K.: Recto-Urethral Fistula Following Perineal Prostatectomy: Report of Four Cases, J. Urol. **46**:699-706 (Oct.) 1941.

52. Emmett, J. L.: Urinary Incontinence of Fifteen Years' Duration in a Tabetic Patient Relieved by Transurethral Resection: Report of a Case, Proc. Staff Meet., Mayo Clin. **16**:728-730 (Nov. 12) 1941.

not a constant dripping of urine but apparently was an involuntary type of urination. Neurologic examination revealed evidence of tabes dorsalis. Cystoscopic examination disclosed moderate relaxation of the vesical sphincter muscles. The urethra in the region of the penoscrotal angle was markedly contracted and would admit only a small resectoscope. This narrowing was the result of large caliber stricture which followed previous urethritis. There was moderate enlargement of all three lobes of the prostate gland. About 8 Gm. of tissue was resected, after which the patient voided urine normally.

Henline [53] states that each of the three main types of prostatic operation—prostatic resection, suprapubic prostatectomy and perineal prostatectomy—has its place, yet none should be used to the exclusion of the others. The origin, the extent and the location of prostatic disease always should be considered in selection of the proper operative approach to relieve the patient completely and permanently of his prostatic disease. Prostatic calculi can be more completely removed by subtotal perineal prostatectomy with less morbidity and more nearly permanent cure than by other methods. Perineal exposure with removal of the posterior lobe of the prostate gland is the only method by which an early malignant neoplasm of this portion of the prostate gland can be removed. Newer perineal prostatic operations permit adequate control of hemorrhage, offer a means of complete removal of the diseased prostate gland, often prevent postoperative morbidity and provide greater assurance of permanent lasting relief from prostatism.

Resection.—Nesbit and Conger,[54] in discussing their studies on the loss of blood during transurethral prostatic resection, state that the excessive loss of blood which occurs during any surgical procedure tends to increase the hazard of operation and to influence adversely postoperative morbidity. Candidates for prostatectomy frequently are elderly and debilitated men who often have some degree of renal insufficiency. Excessive loss of blood resulting from well executed transurethral resection among such patients may impair the general recuperative powers and resistance to infection, even though the patients escape immediate surgical shock. To secure data on the actual loss of blood during operations among these patients, a series of 100 consecutive cases in which transurethral resection was done was studied, and the loss of blood was estimated.

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53. Henline, R. B.: The Surgical Treatment of Prostatic Disease, J. A. M. A. **117**:2030-2034 (Dec. 13) 1941.

54. Nesbit, R. M., and Conger, K. B.: Studies of Blood Loss During Transurethral Prostatic Resection, J. Urol. **46**:713-717 (Oct.) 1941.

In this series of cases a fair cross section of prostatic disease was obtained. There were 71 cases of benign prostatic hypertrophy, 21 cases of carcinoma of the prostate gland and 8 cases of contracture of the vesical neck. In 3 cases, reresection was done. Thirty-nine patients were operated on by the chief of the service; the rest were operated on by the resident surgeons.

Operative losses of blood varied greatly; the amounts ranged from as low as 4 cc. in a case of contracture of the vesical neck to 1,254 cc. in a case of particularly vascular benign hypertrophy. The average loss of blood in this series was 169 cc. Forty-six per cent of all patients lost less than 100 cc. of blood. These were patients who had smaller glands and median bars. Twenty-two per cent of the patients lost more than 250 cc. These patients had larger prostate glands (average, 35.4 Gm.), and the condition in all was benign, except in 4 who had cancer.

Determinations of the postoperative loss of blood were not carried out in Nesbit and Conger's series because urinary pigments made colorimetry inaccurate. They say, however, that in 1937, Hubly studied a series in which transurethral resection had been done in 53 cases at the Mayo Clinic and that he estimated both the operative and the twenty-four hour postoperative loss of blood by spectrophotometric and photelometric methods. He found, they say, that patients lost about two-thirds again as much blood during the first twenty-four hours postoperatively as was lost during the operation itself. Nesbit and Conger believe these figures to be highly significant and speculate that the total loss of blood approximated perhaps twice the operative loss. Thus, they conclude that the 22 per cent of their patients who lost more than 250 cc. of blood during operation, as previously noted, eventually suffered a significantly high loss of blood.

Carcinoma.—Herbst [55] discusses the effects of estradiol dipropionate and diethylstilbestrol on malignant prostatic tissue. These substances apparently relieve the pain caused by local prostatic malignant tissue and metastasis of carcinoma to bone and modify the physiology of breast and prostatic tissue in a demonstrable manner. The ultimate result of this action was not predictable at the time of Herbst's report, and pathologic microscopic studies have not been possible. Relief of dysuria and nocturia and reduction in the amount of residual urine are early responses to this form of treatment, he states.

As time goes on, Herbst says, it is to be hoped that observations such as those he mentions will serve to stimulate progress in specific control of tissue by the administration of these or other yet to be produced

55. Herbst, W. P.: The Effects of Estradiol Dipropionate and Diethyl Stilbestrol on Malignant Prostatic Tissue, Tr. Am. A. Genito-Urin. Surgeons **34**:195-202, 1941.

substances. It should be fully realized in the meantime, however, that the complexity of the biochemical problem is such that it may be a long long time before completely satisfactory control of tissue can be an accomplished fact.

De Vries,[56] in discussing the differential diagnosis of carcinoma of the prostate gland with skeletal metastasis and osteitis deformans, states that digital examination of the prostate gland per rectum will be sufficient for diagnosis in 90 per cent of the cases; but because some malignant lesions originate and are situated in parts of the prostate gland other than the posterior lobe, cystoscopy should not be neglected. Biopsy may be desirable for confirmation of the diagnosis, but unless results are positive, biopsy in itself should not be relied on. Aspiration biopsy is less reliable than other methods. Roentgen examination of the bones should be extensive and directed specifically to the study of bone, both distribution and local appearance being diagnostic factors. So far as distribution is concerned, although the spinal column, the pelvis and the long bones may be affected by either condition, a lesion of the skull is most likely to be Paget's disease, and a costal lesion is most likely to be carcinoma. In the matter of local appearances, thickening, increase of coarse trabeculations, bowing and deformity, increased cortical density and decrease of the marrow space are the important observations in Paget's disease; whereas absence of these signs with spotty areas of increased density, decreased density or both present is the significant characteristic of metastatic carcinoma of the prostate gland. It is well to remember also the possibility that both lesions can occur simultaneously in the same person.

Leiomyosarcoma.—Prince and Vest [57] report a case of leiomyosarcoma of the prostate gland and state that leiomyosarcoma is a definite entity which differs pathologically and clinically from other types of sarcoma of the prostate gland. Among adult persons, leiomyosarcoma is of a somewhat lower degree of malignancy than is sarcoma of the prostate gland of other types. The average duration of life in the acceptable cases of leiomyosarcoma of the prostate gland has been found to be three and two tenths years among patients more than 20 years old and two and a half months among patients less than 20 years old. As far as Prince and Vest know, they say, this is the first instance in which the diagnosis has been made preoperatively and in which complete surgical

56. de Vries, J. K.: The Differential Diagnosis of Carcinoma of the Prostate with Skeletal Metastases and Osteitis Deformans (Paget's Disease of Bone), J. Urol. **46**:981-996 (Nov.) 1941.

57. Prince, C. L., and Vest, S. A.: Leiomyosarcoma of the Prostate: Report of a Case and Critical Review, J. Urol. **46**:1129-1143 (Dec.) 1941.

removal of the prostate gland has been carried out intentionally for sarcoma. The functional results which followed radical operation in their case were excellent, and the patient was apparently completely well and free from metastasis a year after the operation.

Abscess.—Hamer and Wishard [58] report an unusual case of prostatic abscess. The patient, 64 years old, who had low grade nonspecific prostatitis, returned after a vacation complaining of cloudy urine and moderate irritability of the bladder. Massage of the prostate gland yielded the usual secretion, which contained 50 pus cells, more or less, per field under the high power objective. There was no residual urine. After gentle massage of the prostate gland, the patient had a chill. Inflammatory enlargement of the left lobe of the prostate gland was noted, but no evidence of fluctuation could be found. Each rectal examination was followed by chills and fever. Sulfanilamide drugs improved the clinical picture not at all. Within another week, signs of cardiac enlargement appeared; these were followed shortly by "congestive heart failure and terminal pneumonia within eighteen days of the onset." Necropsy disclosed a prostate gland slightly larger than normal, in the left lobe of which was a completely sealed-off abscess 5 mm. in diameter. Smears of material obtained from this abscess contained gram-positive cocci. Small, thrombosed veins and many lymphatic glands were found along the course of the great vessels, as far as the mediastinum. Acute fibrinous pericarditis and an incidental aneurysm of the aortic arch also were seen.

URETHRA

Carcinoma.—Wishard [59] has brought the bibliography of primary carcinoma of the male urethra up to date through May 31, 1941. The total number of instances substantiated by biopsy is 166. Wishard includes an additional instance in which carcinoma of the male urethra was treated by radium, roentgen rays and electrocoagulation with apparent success (for two years at least) without evidence of recurrence. He makes no claim, however, of originality for the method.

Dodson [60] reports 3 cases of carcinoma of the urethra. In the first of these, the patient was an elderly man whose urethra had been divided and transplanted into the scrotum because of stricture which had

58. Hamer, H. G., and Wishard, W. N., Jr.: An Unusual Case of Prostatic Abscess, Tr. Am. A. Genito-Urin. Surgeons **34**:261-264, 1941.

59. Wishard, W. N., Jr.: Primary Carcinoma of the Male Urethra, Tr. Am. A. Genito-Urin. Surgeons **34**:265-271, 1941.

60. Dodson, A. I., in discussion on papers of Barringer, Nesbit and Cummings,[47] Hamer and Wishard [58] and Wishard,[59] Tr. Am. A. Genito-Urin. Surgeons **34**:274-275, 1941.

followed gonococcic infection. When he was seen he was almost moribund, and external ureterostomy was done for drainage in the hope that some sort of treatment of the tumor could be instituted later. He died rather quickly. Necropsy disclosed that squamous cell carcinoma had involved the urethra and the scrotum.

The second patient had no history of gonorrhea or previous stricture. He had consulted a urologist, who had resected the prostate gland; this he believed was the source of the bleeding. Later, periurethral abscess developed. Resection of the perineal portion of the urethra, including the penis, was done, and repair was made by the turning down of a flap of the urethra posteriorly and utilization of the subcutaneous structure of the scrotum to fill in and cover over in front.

The third patient had a history of stricture which had been treated after an attack of gonorrhea and which occurred in association with periurethral abscess. Resection and reanastomosis of the corpora and the urethra were done for this patient.

An outstanding feature in these 3 cases was an abscess at the site of the cancer, and this abscess was similar to the type of perineal abscess that is found in cases of advanced stricture of the urethra.

TESTES

Tumors.—Hinman, Johnson and Carr [61] state that all testicular tumors should be treated by immediate orchidectomy, followed by adequate roentgen therapy. Radical removal of the regional lymph zone has been discontinued because careful study of the records of all their patients throughout the years convinced them that not infrequently metastasis occurs across the midline or even above the surgically available lymph zone before it is demonstrable in the chain of lymph nodes which formerly was removed.

The presence of abnormal amounts of hormone in the urine suggests a bad prognosis.

It seems evident that all malignant testicular tumors are so closely related that only a simple clinical classification of them is justifiable.

The malignancy of a given testicular tumor depends on the degree of the differentiation of cells, and this is not constant in any given case.

Transplantation.—Kearns [62] carried out autoplastic testicular transplantation for a patient 23 years old, after accidental castration. The

61. Hinman, F.; Johnson, C. M., and Carr, J. L.: The Clinico-Pathologic Classification of Tumors of the Testis in Relation to Prognosis, Tr. Am. A. Genito-Urin. Surgeons **34**:211-225, 1941.

62. Kearns, W. M.: Testicular Transplantation: Successful Autoplastic Graft Following Accidental Castration, Ann. Surg. **114**:886-890 (Nov.) 1941.

patient's testes, which after accidental removal had been preserved, were then transplanted. Each section, which was about 2 mm. thick, was implanted in the scrotal wound and covered with the flaps of the remaining scrotal skin. One section of epididymis also was implanted. Successful graft resulted. Observation of this patient for two and a half years demonstrated that regeneration of the prostate gland and normal sexual function had resulted and that normal results of clinical and laboratory tests had persisted. Kearns recommends this procedure for replacement of testicular tissue which is lost in warfare.

Ectopy.—Thompson and Heckel [63] state that there are two causes of failure of descent of the testis: (1) glandular deficiency and (2) anatomic abnormalities.

Since the testis can function normally only when it is enclosed in the scrotum, Thompson and Heckel are of the opinion that it is logical to assume that the earlier it is brought into the scrotum, the more likely it is to be normal. By means of glandular therapy it is possible to determine at an early age whether or not operative procedures will be necessary. If there is no mechanical obstruction, the testis will descend by means of glandular therapy alone. If it does not descend, operative procedures will be necessary and can be facilitated by enlargement of the parts as produced by glandular therapy. Chorionic gonadotropin is the most satisfactory therapeutic agent in most instances. Treatment involves use of the combination of glandular therapy and surgical procedures. The age of the patient and the situation of the testis exert some influence on the success of glandular therapy. The incidence of successful results is higher before than after the patient has reached the age of puberty.

Thompson and Heckel were able to produce testicular descent in only 2 of 34 cases in which the location of the testes was intra-abdominal. The majority of successful results were obtained when the testes were located either in the inguinal canal or outside the canal. Thompson and Heckel are uncertain as to how early treatment should be carried out, but they believe observations suggest that therapy should be commenced when the patient is still at an early age.

It is important, they say, to distinguish between true cryptorchidism and pseudocryptorchidism (migratory testes). Migratory testes descend spontaneously at the time of puberty and require no treatment. The inclusion of migratory testes in studies of glandular therapy has tended to exaggerate the percentage of successful results obtained in true cryptorchidism, Thompson and Heckel believe.

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63. Thompson, W. O., and Heckel, N. J.: Endocrine Treatment of Cryptorchism, J. A. M. A. **117**:1953-1956 (Dec. 6) 1941.

Counseller [64] states that the age of the patient when he presents himself for the treatment of cryptorchidism has a definite influence on the type of surgical procedure to be used. The site and the position of the testis also are determining factors. A much higher incidence of indirect inguinal hernia on the affected side was noted than had been previously reported, although when the group is considered as a whole the incidence was essentially the same as that noted by previous authors.

Surgical procedures for the correction of cryptorchidism must be varied to suit the particular case with regard to unilaterality, bilaterality and the position of the testes. When it is desirable to develop a scrotum and to maintain the testes for indefinite periods in a fixed position without tension, the Meyer-Torek operation is most satisfactory. In most other instances, the Cabot operation is generally applicable. In a relatively few cases in which there is a normally developed scrotum and in which the testes can be easily placed in the scrotum, the Bevan operation may be indicated.

Castration must be considered as a surgical procedure when cryptorchidism is encountered. Castration usually is done for atrophy, for inability to add sufficient length to the cord, for tumor or for previous injury. It is not commonly done when the patient is in the first and second decades of life, but generally is performed when he is beyond the third decade.

Endocrinotherapy for cryptorchidism should be confined to a relatively few patients and should be employed, even then, only if spontaneous descent seems improbable. It can be used with benefit in cases of hermaphrodism or hypogonadism, Counseller says.

Heckel [65] states that, in contrast to the enthusiastic reports of highly successful results from hormonal therapy for cryptorchidism, he has not been able to bring undescended testes into the scrotum in more than 20 per cent of the total number of cases. He has never been able to cause descent in any instance of intra-abdominal testes.

It seems that in the proper management of the problem of undescended testes, two classifications should be considered. In the first group are those patients who have an undescended testis or testes associated with some endocrine disturbance, such as Fröhlich's syndrome, hypopituitarism or genital infantilism from whatever cause. In this group endocrinotherapy plays an important role in the management of the condition. The type of endocrine preparation to use depends on the

64. Counseller, V. S.: Ten Years' Experience in the Management of Cryptorchidism, J. Urol. **46**:722-731 (Oct.) 1941.

65. Heckel, N. J., in discussion on Counseller.[64]

ability of the testes to respond to stimulation. If the testes can respond to stimulation, then chorionic gonadotropin is the therapeutic agent of choice. If not, androgens should be used.

In summary, Heckel says that it seems that the high percentage of good results (60 to 70 per cent, on an average) reported from the use of endocrinotherapy for cryptorchidism is greatly exaggerated and that, as Counseller has pointed out, perhaps the reason for this is the incorrect diagnosis of undescended testes and the inclusion of the so-called migratory testes, or those which migrate in and out of the scrotum and tend to remain in the scrotum at or near the time of puberty. Patients with this sort of cryptorchidism make up the second group. Heckel says that no treatment of migratory testes is indicated. The greatest field of usefulness of endocrinotherapy for undescended testes is among those patients who have some type of endocrine disturbance associated with this condition and among those in whom the failure of descent is not due to mechanical factors. The management of true undescended testes, however, is still a surgical procedure.

Sex Hormones.—Heckel [66] states that alpha estradiol benzoate, like testosterone propionate, produces sterility in man. The degenerative changes in the seminiferous tubules caused by these two substances are similar. Whereas testosterone propionate has no effect on the volume of seminal fluid, alpha estradiol benzoate produces a spectacular decrease in its volume. Since the seminal fluid in man is composed mostly of the secretions from the prostate gland and the seminal vesicles, Heckel has deduced that the cause for this decrease in volume is due to the influence of this material on the secretory mechanism of these two glands. Other untoward effects observed to result from the use of alpha estradiol benzoate were: hypertrophy of the breasts, enlargement of the nipples and the development of impotency.

Tumor.—Gilbert [67] analyzes 58 of the detailed reports concerning a total of 65 patients among whom malignant tumor of the testis developed after orchidopexy. The interval between orchidopexy and development of the tumor averaged twelve years for the unicellular type and five years for teratoid tumor. In 49 cases of the entire group in which it was recorded, the average interval between orchidopexy and recognition of the tumor was ten years. The duration of recognized tumor growth,

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66. Heckel, N. J.: A Comparative Study of the Effect of Sex Hormones upon the Function of the Human Testes, Tr. Am. A. Genito-Urin. Surgeons **34**:237-247, 1941.

67. Gilbert, J. B.: Studies in Malignant Testis Tumors: V. Tumors Developing After Orchidopexy; Report of Two Cases and Review of Sixty-Three, J. Urol. **46**:740-747 (Oct.) 1941.

to the time of surgical intervention, as stated in 45 cases, averaged sixteen months. There were 34 unicellular tumors and 19 teratoid tumors. The remaining 12 tumors were either of miscellaneous types or not definitely classified. In 54 cases (83 per cent), the tumor-bearing testicle was situated in the scrotum, whereas in 11 (17 per cent), it was located ectopically (7 inguinal and 4 abdominal). Among the majority of the patients (43 or 66 per cent), the tumor was primary and operable, whereas among only 15 (23 per cent) it was inoperable on admission of the patient. Of the 34 patients who had unicellular tumors, 16 (47 per cent) were alive and apparently well one and a half years later, whereas 5 (15 per cent) were alive three years later, and 1 of these was alive five years after surgical intervention. Of the 19 patients who had teratoid tumors, 3 (17 per cent) lived three years after the operation, and only 1 of these was alive five years after the operation.

Gilbert says the survival rate in this group is poor. Only two authors have reported arrest of metastatic disease by means of combined surgical treatment and irradiation, and two others have reported five year survivals achieved by operation alone; in 1 case the lesion was seminoma and in the other teratoma.

On the basis of the results of his study, Gilbert concludes that the ectopic testis should be adequately fixed in the normal scrotal position. Surgical replacement to the abdomen is condemned. The predominating pathologic type is unicellular. Teratoid tumors in his series developed seven years earlier than unicellular tumors after orchidopexy and were consistently more fatal. Surgical trauma incidental to testis fixation and herniorrhaphy does not appear to favor the genesis of tumors.

URINARY CALCULI

Sanford and Barnhart[68] state that renal stones which are studied and classified preoperatively as being too large to pass down the ureter should be removed surgically unless serious contraindications to operation are present. The danger of infection and the potential threat that a stone might move to an obstructive position with the almost immediate production of acute symptoms is constantly present. In contrast to this anticipated occurrence, appreciation of the opposite possibility also is important. A patient who has a single stone of fairly large size situated in the true pelvis of the kidney may be surprisingly free from symptoms. Delayed operation, intentional or otherwise, is

68. Sanford, J. H., and Barnhart, W. T.: The Surgical and Nonsurgical Management of Renal and Ureteral Calculi, J. Urol. **46**:1061-1069 (Dec.) 1941.

occasionally followed by disaster. Some months later the stone may have migrated down the ureter and silently destroyed the kidney. Unilateral or bilateral branched renal calculi are conspicuously devoid of pronounced symptoms but consistent in the gradual and progressive damage to renal function which they cause. Early operation in the presence of unilateral or bilateral branched renal calculi is advisable in most cases. Sanford and Barnhart say that a large percentage of ureteral calculi that can be accommodated by the ureter are recoverable by cystoscopic manipulative methods. They say that they prefer the ureteral catheter or the use of catheters left in place for twenty-four to forty-eight hours to any other method. In cases in which infection is resistant, with partial or complete blockage of the kidney, surgical intervention is demanded after several attempts at conservative measures have failed. Delay in this type of case is hazardous. Incision of the ureteral orifice to facilitate passage of stones in the extreme lower part of the ureter has proved to be immensely valuable.

Of 200 patients with calculi in the upper part of the urinary tract seen by Sanford and Barnhart in the six years prior to their report, 64 had renal calculi, 125 had ureteral calculi and 11 had both renal and ureteral calculi. Those who had renal calculi were treated in the usual manner, i. e., by either observation or operation. In the latter case, pyelolithotomy, nephrolithotomy or nephrectomy was done. In the 125 cases of ureteral calculi, surgical removal was done in 17, and the calculus was passed or extracted from the ureter in 108 cases.

In 86.4 per cent of the cases of ureteral calculi, operation was not necessary, and Sanford and Barnhart believe that such conservatism was justified. They say, however, that the urologic surgeon can be too conservative.

UROLOGIC COMPLICATIONS

Ewert [69] states that postoperative genitourinary complications after surgical treatment of the large bowel are most common after removal of the rectal portion of the large intestine. The complications may be of such major importance that they definitely prolong the patient's convalescence. Infections of the urinary tract account for most of these complications and may be interrelated with the neuromuscular function of the bladder in many instances. Paralysis of the bladder must be treated intelligently if the upper portion of the genitourinary tract is to be spared irreparable damage. Since many patients continue to have

69. Ewert, E. E.: A Comparative Analysis of the Urological Complications Following Large Bowel Surgery, J. Urol. **46**:764-776 (Oct.) 1941.

pyuria after they are dismissed, even though they may have no symptoms, persistent reexamination to determine the cause and the treatment is necessary for months. The cure of the cancer is the major role; the treatment of the urologic complications frequently is the minor one.

Seaman and Binnig [70] say that urologic complications occurring in the presence of cancer of the rectum and due either to the disease itself or to the operation incident to the removal of the neoplasm are relatively common. They vary in occurrence and severity and are more often than not caused by destruction of sympathetic or parasympathetic pathways or some degree of trauma and possibly also by infection. Infection is a common accompanying problem, because of the nervous disturbance and because of the altered position of the floor of the bladder in the pelvis.

An appraisal of the present operative technic is suggested for avoidance of trauma to the lower part of the urinary tract and its nerve supply. There is apparent evidence that the suggestion has merit. The authors emphasize the importance of urologic orientation before and after operations, and they stress the need for the carrying out of cystometric studies for each patient. The present day concept of neuroanatomy and neurophysiology is offered as a background to understanding the mechanism of dysfunction of the bladder.

VAGINITIS

Rice, Cohn, Steer and Adler [71] report results of their recent investigations on gonococcic vaginitis. Since the inception of their study, 381 (22.2 per cent) of 1,715 children they examined were found to have gonococcic vaginitis. The infected children were examined once a week until the results of diagnostic laboratory procedures were negative and remained thus for about eight successive weeks, after which the children were examined at monthly intervals.

Nonspecific vaginitis and gonococcic vaginitis can be distinguished only by means of smear and/or culture. Culture is far superior to the making and examining of smears, especially if the chronic stage of the infection is present.

It was arbitrarily agreed by the authors that children, to be considered cured, must be clinically normal and that at least seven smears and cultures made consecutively during a period of at least sixteen

70. Seaman, J. A., and Binnig, C.: Urological Complications of Cancer of the Rectum, J. Urol. **46**:777-787 (Oct.) 1941.

71. Rice, J. L.; Cohn, A.; Steer, A., and Adler, E. L.: Recent Investigations on Gonococcic Vaginitis, J. A. M. A. **117**:1766-1768 (Nov. 22) 1941.

weeks must contain no gonococci. Prolonged study revealed that this criterion was satisfactory for 92.2 per cent of the 204 patients studied intensively.

Forty-one children were observed who did not receive any form of treatment. Some recovered within a short time; 54 per cent recovered by the tenth week, and 87 per cent recovered by the twenty-eighth week, after the beginning of observation. This, the authors believe, is definite evidence that spontaneous cure of the disease may occur among the majority of patients.

Thirty-three children were treated with estrogenic substances (amniotin and diethylstilbestrol). The 12 (36 per cent) who were cured were treated for an average of fifty-four and five-tenths days. Comparison of results with the results obtained in control series shows that, bacteriologically, cure was no more frequent among patients who received this form of therapy than it was among the untreated patients. Definite clinical improvement, however, followed shortly after the institution of treatment.

Fifty-three children were treated with sulfanilamide. The 23 (43 per cent) who were cured were treated for an average of nine and six-tenths days. This drug gave definitely better results than would be expected without treatment.

Because the results of therapy obtained with each drug were approximately the same, the 20 children treated with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and the 57 treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) were combined into a single group. The 67 (87 per cent) who were cured received treatment for an average of six and seven-tenths days. These drugs were effective against rectal infection when it was present. Sulfathiazole appeared to be the drug of choice, because it produced fewer toxic reactions (nausea and vomiting) than did sulfapyridine. For the present, the authors suggest that children receive ½ grain (0.032 Gm.) per pound (0.5 Kg.) of body weight per day, with a maximum of 30 grains (2.0 Gm.) per day for from seven to ten days.

Vaginitis is generally believed to be extremely contagious, requiring only superficial contact for its transmission. Outbreaks in epidemic form have been described. Rice, Cohn, Steer and Adler, however, say that the question of widespread dissemination of this disease in public places requires reconsideration. In more than five years of search no evidence was found of an epidemic in a New York school, although many children who had recently acquired infections had attended these schools before a diagnosis was made. During the course of this study

no instance of an epidemic in any institution or orphanage was discovered.

URINARY ANTISEPTIC AGENTS

Therapy with Sulfanilamide and Its Derivatives.—Carroll, Kappel and Allen [72] state that sulfathiazole and the sodium salt of sulfathiazole are found to be of little value in the treatment of prostatitis. In the treatment of pyelitis, pyelonephritis, ureteritis, cystitis due to urinary retention, cystitis associated with Hunner's ulcers and nonspecific urethritis, sulfathiazole and its sodium salt, although they are valuable adjuncts in treatment, do not provide permanent cure in a large percentage of cases of these diseases. Relief of these conditions depends on proper diagnosis of the causative factors involved and the correction of them.

The use of the drug is limited also, because of the toxic or allergic reactions to it which comprise 15 per cent of the urinary infections encountered. The confusion created by so-called drug fever and the uremic symptoms caused by the drug act as deterrents to the prescription of this drug. The mode of application has been enlarged from that of oral administration to that of local application of the powder in wounds postoperatively and into necrotic and abscessed cavities as well as to ulcers and infections about the genitalia.

Deakin and Patton [73] state that approximately 19 out of 20 men who have gonorrhea can be rendered noninfectious by the oral administration of 20 Gm. of sulfathiazole in a five day period. Sulfathiazole is more efficient than sulfanilamide or sulfapyridine in the oral treatment of gonorrhea among men. When this dosage is employed, risk in the use of sulfathiazole as a form of ambulatory treatment of gonorrhea is minimal. Lack of cooperation on the part of the patient, previous therapy with the sulfanilamide drugs and the presence of severe complications before treatment are the chief causes of chemotherapeutic failure in this particular disease.

Herrold,[74] in discussing Deakin and Patton's paper, states that he and John Henry had administered sulfathiazole to approximately 400 male patients suffering from gonorrhea at the Illinois Social Hygiene

72. Carroll, G.; Kappel, L., and Allen, H.: Sulfathiazole and Its Sodium Salt: Effectiveness and Limitations in Clinical Practice, J. Urol. **46**:1033-1042 (Nov.) 1941.

73. Deakin, R., and Patton, J. F.: Sulfathiazole in the Treatment of Two Hundred Cases of Male Gonorrhea, J. Urol. **46**:1043-1048 (Nov.) 1941.

74. Herrold, R. D., in discussion on papers of Prien, Crabtree and Frondel, Carroll, Kappel and Allen and Deakin and Patton, J. Urol. **46**:1049-1050 (Nov.) 1941.

Clinic. They completed their study on the group treated between May 15 and Dec. 15, 1940. There were 271 patients in this group, of whom 148 received exactly the same dosage as members of the group of Deakin and Patton, namely, 4 Gm. a day for five days. Herrold says that he and Henry had accepted this as their standard dosage schedule. Two hundred and six of the patients were seen for periods longer than thirty days, and 149 (about 55 per cent) were seen for periods longer than sixty days. Hence, there remained 65 patients (approximately 24 per cent) who were transferred, left the city or deliberately lapsed treatment before they had received it for thirty days.

Relapse or reinfection was noted among 36 patients during the course of observation, so that if everything is taken into consideration, it is believed that between 80 and 90 per cent of male patients with gonorrhea can be cured by the administration of one course of sulfathiazole. Herrold says that in the clinic in question, local treatment is given by the physicians because it has aided in obtaining the cooperation of the patients. It has been found also that when sulfathiazole is used, a higher percentage of failures occurs among patients in whom previous treatment with other sulfanilamide drugs has failed to cause improvement. Little can be expected from the practice of repeating the course of treatment with sulfathiazole for patients with infections which clearly have been refractory to sulfanilamide drugs, but Herrold says that he does not agree that a second course should not be instituted for those patients who previously have received no chemotherapy other than one course of sulfathiazole and who have experienced clinical relapse within a week after completion of the first course. A number of such patients, he says, have been cured by receiving a second course of therapy with either sulfapyridine or sulfathiazole.

Herrold has seen also many patients who did not respond clinically to therapy with sulfanilamide during the first ten days of their infection; when, however, the medication was changed to either sulfapyridine or sulfathiazole, prompt favorable response was obtained, a response which was similar to that obtained among patients to whom chemotherapy had been administered previously. Sulfathiazole is the drug of choice over sulfapyridine because of the smaller incidence of certain toxic reactions, particularly those referable to the gastrointestinal tract, which accompany its use.

Fletcher, Gibson and Sulkin [75] carried out a carefully controlled study among 194 hospitalized female patients with gonorrhea. Two methods of treatment were employed. The first consisted of the oral

75. Fletcher, P. F.; Gibson, O. J., and Sulkin, S. E.: Sulfathiazole in the Treatment of Gonorrhea in Women, J. A. M. A. **117**:1769-1773 (Nov. 22) 1941.

administration of 60 grains (4 Gm.) of sulfathiazole daily for five days and the insertion of a vaginal suppository containing beta lactose and boric acid. The suppository was inserted once a day for twelve consecutive days. The second method of treatment consisted of the administration of the same dose of sulfathiazole but omission of the vaginal suppository.

Toxic manifestations were noted in 13 cases (6.7 per cent) and were sufficiently severe in 2 of them to necessitate termination of treatment. The most pronounced reactions observed were manifested as a painful urticarial rash in 1 case and as uncontrollable nausea and vomiting in a second case. All cutaneous manifestations disappeared within seventy-two hours after the administration of the drug had been discontinued.

Every case was classified as chronic gonorrhea with the exception of 2 in which there was acute inflammation of the cervix, the urethra and both adnexa associated with a severe febrile reaction. In the cases classified as chronic gonorrhea there were no symptoms.

Forty-five per cent of the patients had a gonorrheal infection of the cervix alone. In 12 per cent, only the urethra was involved, whereas in 43 per cent both cervical and urethral infections were present. "Every patient in whom the pelvic adnexa were present showed some type of chronic inflammatory condition," the authors remark.

Detailed analysis of the results obtained in the two groups of patients revealed that beta lactose therapy had had no influence on the treatment of gonococcic infection. The authors conclude:

> . . . Ninety-one and two tenths per cent of the total number of patients under observation at the end of the "quarantine parole" period (twelve weeks) were considered "clinical cures." It may therefore be assumed that sulfathiazole in the treatment of gonococcic infections in the female is highly effective in a great majority of cases.

Peterson and Beuchat [76] report the following impressions after studying and treating 178 patients with gonorrhea:

About half of the patients who receive sulfanilamide will have an immediate adequate response and will be cured. The other half will have an inadequate response.

It appears that the immediate adequate response of the patient to sulfapyridine is greater than his response to sulfanilamide. Sulfapyridine therapy in cases in which the infection has resisted sulfanilamide is efficacious. Among patients with gonorrheal epididymitis and arthritis, the response to sulfapyridine therapy is much better than the response to sulfanilamide.

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76. Peterson, D. B., and Beuchat, E. S.: Treatment of Gonorrhea at Fitzsimons General Hospital: A Study of Cases from Sept. 1, 1938 to Oct. 31, 1940. J. A. M. A. **118**:129-132 (Jan. 10) 1942.

Artificially produced fever is the most efficacious treatment for gonorrhea but has definite disadvantages in that it is expensive and is of danger to the patient. This danger is increased if previous medication with sulfanilamide has been carried out, and almost all patients with gonorrhea have been so treated before they reach a hospital where fever therapy is available. Fever is the standard of good treatment in cases of gonorrheal arthritis.

Patients who do not exhibit an adequate response to initial treatment with sulfanilamide by the fourth day should receive either fever therapy or sulfapyridine.

Welebir and Barnes [77] treated 200 patients who had bacillary infection of the urinary tract with sulfacetimide (paraaminobenzenesulfonylacetylimide). The percentage of recoveries was 85.5; 12.5 per cent of the patients exhibited improvement, and 2 per cent exhibited no response to the drug.

Sulfacetimide has been more effective in the treatment of this type of infection of the urinary tract than have sulfanilamide and the mandelates. In 80.9 per cent of the cases in which the infection had been resistant to sulfanilamide, recovery occurred when sulfacetimide was administered; in 73.3 per cent of the cases in which the infection had been resistant to the mandelates and in all in which it had been resistant to sulfathiazole, recovery occurred when sulfacetimide was used.

There were toxic reactions in 4 per cent of the patients in this series. After discontinuance of the use of the drug, the reaction disappeared within from one day to six days.

The results of this clinical investigation show, the authors say, that sulfacetimide is effective and superior to other sulfanilamide drugs in the treatment of bacillary infections of the urinary tract.

Kornblith, Jacoby and Chargin [78] treated a series of 175 ambulatory patients encountered consecutively and having chancroid infection with sulfanilamide and sulfathiazole.

Identification of the haemophilus of Ducrey on smears stained by the Unna-Pappenheim method was found to be the most important single diagnostic criterion of chancroidal infection. The haemophilus of Ducrey was identified in 88.5 per cent of the cases in smears made routinely with material obtained from chancroidal ulcers. The intradermal reaction to Ducrey vaccine proved to be specific and was found to be positive in about 95 per cent of cases. The authors write:

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77. Welebir, F., and Barnes, R. W.: The Use of Sulfacetimide in Bacillary Infections of the Urinary Tract, J. A. M. A. **117**:2132-2135 (Dec. 20) 1941.

78. Kornblith, B. A.; Jacoby, A., and Chargin, L.: Chancroid: Treatment with Sulfathiazole and Sulfanilamide, J. A. M. A. **117**:2150-2153 (Dec. 20) 1941.

The Ducrey vaccine is more important when the results are negative, to exclude active chancroidal disease. When the reaction is positive it often indicates a past, healed infection.

The reaction to Ducrey vaccine remained positive in all cases after complete healing of the active lesion had taken place.

Chancroidal buboes were present in about 42 per cent of the cases.

Sulfanilamide was administered orally to 150 patients for fourteen days; a total of 45.6 Gm. (760 grains) in divided doses was found to be adequate. Sulfathiazole was administered orally to 25 patients for ten days; a total of 20 Gm. (300 grains) in divided doses sufficed.

All definitely proved chancroidal infections were healed by means of chemotherapy. Surgical measures of any description were contraindicated and found unnecessary. Aspiration of the contents of large inguinal abscesses was found to be sufficient in some cases. Spontaneous absorption of small abscesses took place in 5 cases during chemotherapy. The local application of sulfathiazole powder healed superficial chancroidal ulcerations. Two patients suffered a relapse, but the lesion responded promptly to oral therapy with sulfathiazole.

More than half (54 per cent) of the patients in the series were found to be infected with two, three or four venereal diseases during their observation.

Therapy with sulfanilamide and its derivatives can be used as a therapeutic test in the differential diagnosis of chancroid.

Cook [79] reports the results of recent studies with sodium sulfathiazole. The advantages of this form of the drug over its parent substance are: 1. It is more rapidly absorbed. 2. It is less toxic. As it is absorbed more rapidly, it also is excreted more rapidly. Early in the work on sulfanilamide and its derivatives, the use of much smaller doses than were used elsewhere in treating infections of the urinary tract was advocated at the Mayo Clinic. In cases of impaired renal function, sodium sulfathiazole can be used more easily than can other derivatives of sulfanilamide.

The drug was administered to approximately 200 patients with infections of the urinary tract. Every type of organism was present, as well as all types of pathologic change. The gram-negative bacilli are affected equally favorably from the standpoint of therapy, except for Pseudomonas, which is most obstinate to treatment. The gram-positive cocci, with one exception, all are affected satisfactorily, particularly the staphylococci and the micrococci. Str. faecalis is not affected by this drug; this indicates again that this organism is resistant to sulfanilamide and its derivatives. Certain coexisting pathologic changes, such as

79. Cook, E. N.: Sodium Sulfathiazole in the Treatment of Infections of the Urinary Tract, Proc. Staff Meet., Mayo Clin. **16**:717-718 (Nov. 5) 1941.

tumor, calculi and obstruction, will definitely inhibit the action of the drug. This has been found to be true of all other urinary antiseptic agents.

A dose of 20 to 60 grains (1.3 to 4 Gm.) was used daily, and more recently, Cook says, it has not been more than 30 grains (2 Gm.). The drug was administered for six to ten days.

Toxic reactions have been almost nonexistent—a few patients complained of nausea, which usually disappeared within twenty-four to forty-eight hours. Cutaneous reactions were absent except in 2 cases. In both of these cases, the drug apparently produced reactions manifested by fever, general malaise, headache and nausea, as well as by dermatitis. Administration of the drug had to be discontinued in these cases. In few patients was there any elevation of temperature.

The interesting observation after a clinical trial of sodium sulfathiazole was the rather rapid relief of symptoms that occurred after its administration. Cook says that given to a patient suffering with burning, frequent micturition and dysuria, the drug will bring about complete or almost complete relief of symptoms within twenty-four to forty-eight hours in most instances. Cook believes that the rapid absorption and excretion of the drug are responsible for this rapid relief of symptoms.

Prentiss and Kanealy [80] report results of a clinical study of the efficiency and toxicity of sulfacetimide in the treatment of infections of the urinary tract and also results of a comparison of therapy with this drug with therapy with sulfanilamide. The subjects of this study were 135 patients, the first of a group of approximately 400 treated with sulfacetimide within the two years prior to the authors' report. All but 1 were hospitalized, but many were ambulatory.

All medication was administered orally, without an attempt at alteration of the consumption of the fluid. The daily dose for adult patients ranged from 2 to 10 Gm., the average being 4.89 Gm. The daily dose rarely exceeded 6 Gm., and the administration of larger amounts was not continued for more than a day or two. The length of treatment varied from two to twenty-three days; the average was approximately seven days. The amount of the drug administered in the course of treatment varied from 10 to 103 Gm., but the average patient received 32.3 Gm. The most common method of administration was in the amount of 1.5 Gm. given four times daily, but the same amount given three times daily was employed nearly as frequently. Ten to 15 grains (0.65 to 1 Gm.) of sodium bicarbonate was given with each dose of sulfacetimide.

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80. Prentiss, R. J., and Kanealy, J. F.: Sulfacetimide or Sulamyd (Schering): Clinical Study of Efficiency and Toxicity in Urinary Tract Infections and Comparison with Sulfanilamide Therapy, J. Urol. **47**:11-15 (Jan.) 1942.

There were no severe reactions and only relatively few mild toxic reactions. Cyanosis developed in 5 patients, and among these, the condition of 1 was severe, although he exhibited only a trace of methemoglobin. Mild decreases in values for hemoglobin and erythrocytes were noted in 4 patients, but in no instance did anemia develop which required specific treatment or cessation of medication.

Prentiss and Kanealy conclude on the basis of this study and two previous reports on sulfanilamide therapy in a similar group of patients that sulfacetimide is less toxic and more efficient that sulfanilamide in the treatment of infections of the urinary tract.

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